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Clinical Significance of Incidental Pituitary Tc-99m MIBI Uptake on Parathyroid Spect and Factors Affecting Uptake Intensity

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Abstract

Objective: (1)To define a quantitative cutoff value for incidental pituitary Technetium-99m methoxyisobutylisonitrile (Tc-99m MIBI) uptake above which is of clinical importance and (2) to investigate possible factors affecting the intensity of uptake in pituitary adenoma.
Materials and Methods: A retrospective analysis of 55 patients with a simultaneous parathyroid single-photon emission computed tomography and pituitary magnetic resonance imaging were included. Twenty-four patients with pituitary adenoma were chosen as the study group and 31/55 patients who had no signs of a pituitary adenoma were included in the control group. Mean count values (count/pixel) for pituitary region of interest (ROI)/mean value for normal cortical region ROI (P/C) were calculated in both groups. Median P/C values were compared. A cutoff value for P/C was calculated as a quantitative parameter to indicate pituitary tumors. Possible contributing factors in intensity of pituitary Tc-99m MIBI uptake were investigated.
Results: Median P/C ratios were significantly higher in the study group ($p < 0.001$). A cutoff value of 7.675 was found for P/C to have a sensitivity, spesificity, positive predictive value, and negative predictive value 100%, 96.8%, 96%, and 100%, respectively. There was no correlation between investigated factors and degree of pituitary Tc-99m MIBI uptake.
Conclusions: Incidental pituitary Tc-99m MIBI uptake values above 7.675 for P/C are suspicious for pituitary adenoma and can be further investigated clinically and radiologically. Tc-99m MIBI uptake is not affected from the biochemical nature of the adenoma, the therapies received, size, local invasion, or cystic necrotic component of the tumor.

Keywords: Tc-99m MIBI, pituitary gland, incidental findings

Introduction

Tc-99m MIBI is used as a nonspecific tumor agent in evaluation of various types of tumors.[1,2] Dual-phase parathyroid scan by Tc-99m MIBI is used to localize pathological parathyroid glands in hyperparathyroidism.[3] Tc-99m MIBI is a cathionic lypophilic agent, which enters the cell by passive diffusion. Tumoral uptake mechanism of Tc-99m MIBI depends on this electrical charge. After entering the cell, the molecule binds to the negative inner membrane potential of mitochondria. Increased mitochondrial activity is therefore related with increased radiopharmaceutical uptake.[4]

In the center, dual-phase parathyroid scintigraphy by Tc-99m MIBI is frequently performed. The authors routinely perform single-photon emission computed tomography (SPECT) for parathyroid examination, and pituitary region is also included in the region of interest. Incidentally, activity retention in the sellar region is sometimes observed. However, the clinical significance of this uptake is not clear. The aim of this study was to investigate possible factors affecting the intensity of Tc-99m MIBI uptake in the sellar region in pituitary adenoma patients and the clinical importance of incidental pituitary Tc-99m MIBI uptake. A discussion on the necessity of reporting this finding to lead

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the clinician to further investigations targeting pituitary gland will be included.

Materials and Methods

Patients

A total of 440 consecutive patients who were referred to Nuclear Medicine Department for Tc-99m MIBI parathyroid SPECT imaging between June 2014 and June 2015 were investigated. A retrospective analysis of the hospital registry revealed a total of 55 patients who also had undergone a simultaneous pituitary magnetic resonance imaging (MRI) study for various indications (visual disturbances, headache, galactorrhea, abnormal growth rate, pituitary hormone hypersecretion, etc.). Twenty-four patients were enrolled in the study group with the following inclusion criteria: (1) age >18, (2) being refered to dual-phase Tc-99m MIBI parathyroid SPECT for evaluation of hyperparathyroidism, and (3) coexisting pituitary adenoma (either functional or not). Thirty-one patients who had undergone parathyroid SPECT, but had no signs of a pituitary adenoma, were included in the control group. All patients in the control group were clinically evaluated by endocrinology and metabolism specialists. Their physical examinations showed no pathological findings suggestive of pituitary disease, blood hormone levels were in normal ranges, and brain MRI images showed no pathological findings in the pituitary gland. Together with the demographic data of all patients, the type of the adenoma and the treatment the patients in the study group have received were also noted. The study was approved by Institutional Ethics Committee.

Dual-phase Tc-99m MIBI parathyroid SPECT

Twenty mCi (740 MBq) Tc-99m MIBI was injected intravenously. Together with early (15 min) and late (120 min) static planar images of the skull, neck, and upper thorax, SPECT images were acquired 120 min after radiopharmaceutical injection by dual-head gamma camera (Siemens Ecam-signature, 2008) in 128×128 matrix using low energy, high-resolution parallel hole collimator, in 120 projections of 20 s each, with 1.00 zoom.

MRI studies

All patients in the study group had undergone pituitary MRI. In the control group, each patient had undergone brain and/or pituitary MRI. Pituitary MRI examinations were performed with a 1.5 T MRI unit (Philips Achiva, Philips Medical Systems, Eindhoven, Netherlands) with head coil, in supine position. Pituitary MRI protocol included coronal and sagittal T1-weighted pre- and postcontrast turbo spin-echo (TSE) images (TE/TR, 10/400 ms; slice thickness/interslice gap, 2/0 mm), coronal T2-weighted TSE images (TR/TE, 4000/90 ms; slice thickness/interslice gap, 2/0 mm), and 10 dynamic coronal T1-weighted images (TE/TR, 4/200 ms; slice thickness/interslice gap, 1/0 mm).

The highest dimension and volume of the pituitary tumor were noted for each patient. Volume of the tumor was calculated as a multiple of three dimensions in axial, sagittal, and coronal plane and constant 0.523. Histopathological features of the tumors, such as existence of cystic, necrotic, or hemorrhagic components or local invasion, were also evaluated.

Image analysis

Identical rectangular region of interest (ROI) were drawn around pituitary radiotracer uptake and normal cortical tissue on either axial or transverse plane. Mean count values (count/pixel) for each ROI were noted, and mean value for P/C was calculated for every patient in both groups. Special care was taken to exclude physiological choroid plexus activity from the ROIs.

Data and statistical analysis

Descriptive characteristics of the variables were found (mean, median, and frequency). It was checked out if the numeric values complied with a normal distribution. Since the numeric values were not distributed normally, nonparametric tests were used. For comparison of two groups, Kruskall–Wallis and Mann–Whitney U tests were used. The authors carried out a receiver operating characteristic (ROC) analysis to define the cutoff pituitary uptake values, which had the highest sensitivity and specificity in pituitary adenoma. For correlation analysis, because the variables were not distributed normally, Spearman analysis was made. Comparison of categorical variables were made by Chi-square test. p Values <0.05 were considered to be statistically significant. Statistical analysis was performed by ''Statistical Package for Social Sciences—SPSS 17'' (Chicago, ABD).

Results

Twenty-four patients (16 female and 8 male), median age 53.5 (41.5–59.75), were enrolled in the study group. Control group consisted of 31 patients (24 female and 7 male), with median age 62 (56–73) (Table 1). In the study group, there were 6 patients (25%) with a nonfunctioning pituitary adenoma, 10 with acromegaly (41.7%) and 8 with prolactinoma (33.3%). Thirteen patients (54.2%) received no treatment, 6 of them (25%) had undergone surgery, 3 of them (12.5%) were under medical treatment, and 2 of them were (8.3%) under medical treatment following surgery (Table 2). All patients had either a remnant or a recurrent pituitary adenoma indicated by MRI. None of them had a scar tissue following these therapies.

Median P/C ratios were markedly higher in the study group (30.32 range: 20.85–53.94) compared with the control group (1.63 range: 1.22–2.11) ($p < 0.001$).

The power of pituitary uptake values of subjects and control cases in predicting pituitary adenoma patients and healthy cases were compared by a ROC analysis (Fig. 1). A cutoff value of 7.675 was found for P/C to have the highest sensitivity (100%) and specificity (96.8%). All cases in the

Table 1. Descriptive Characteristics of the Patients

	Control group (n = 31)	*Study group (n = 24)*	p
Age	62 (56–73)	53.5 (41.5–59.75)	0.009
Gender			0.375
Male, *n* (%)	7 (22.6)	8 (33.3)	
Female, *n* (%)	24 (77.4)	16 (66.7)	

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Table 2. Distribution of the Patients in the Study Group According to the Nature of the Pituitary Adenoma and the Treatments Received

Nature of the Adenoma	n *(%)*
Nonfunctional	6 (25.0)
Prolactinoma	8 (33.3)
Acromegaly	10 (41.7)
Treatment	
None	13 (54.2)
Operation	6 (25.0)
Medical treatment	3 (12.5)
Operation+medical treatment	2 (8.3)

study group showed a P/C value greater than 7.675, and all but one control subject had a P/C value less than 7.675.

Correlation between MRI findings and Tc-99m MIBI uptake was also investigated. Statistical analysis revealed no significant relationship between the highest dimension of the tumor measured on MRI images or calculated volume and intensity of Tc-99m MIBI uptake in the pituitary region (Table 3). Correlation was found, however, between the size of the tumor and intensity of uptake for patients with tumors less than 1 cm ($p = 0.002$).

Possible relationship between the radiological features of the tumor on MRI and Tc-99m MIBI uptake was studied. Because the number of patients was too small in the subgroups, statistical analysis included comparison of the two groups: patients who had tumors with regular borders and homogenous radiological characteristics and the patients with adenomas, including cystic, necrotic, or hemorrhagic components or local invasion. None of these features appeared to have a statistically significant effect on the degree of radiopharmaceutical uptake (Table 4).

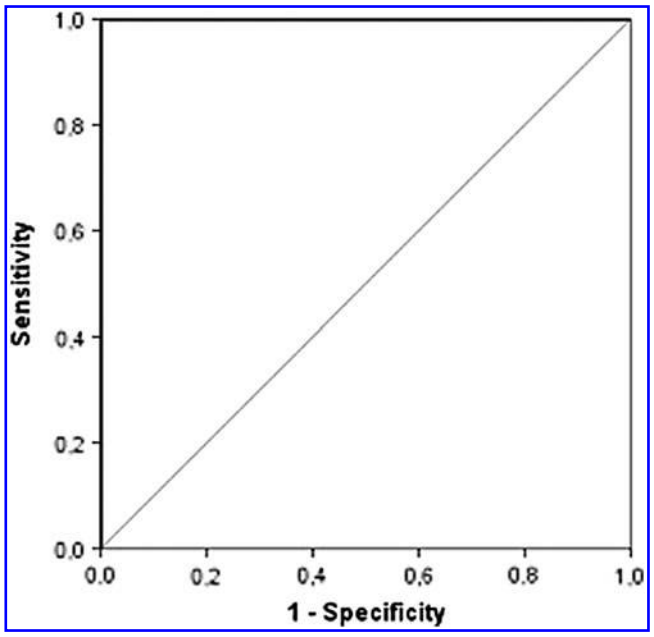


FIG. 1. Demonstration of the ROC curve for a given cutoff value of P/C = 7.675. ROC, receiver operating characteristic.

Table 3. Correlation Analysis Results Between P/C Values and Highest Dimension Measured on MRI and Calculated Tumor Volume

	p	r
P/C × MRI highest dimension	0.258	0.240
P/C × MRI calculated volume (overall)	0.111	0.333
P/C × MRI calculated volume (microadenomas)	0.002	0.787

MRI, magnetic resonance imaging.

Thirteen patients have received no treatment, but the rest of them underwent various types of treatment. When the patients were distributed into subgroups, the number of patients in each group was very small. Thus, statistical analysis was made on two groups: the patients who had received no treatment yet and the patients who received any treatment mentioned above. Correlation analysis revealed that there were no statistically significant differences in Tc-99m MIBI uptake of the pituitary tumors between two groups (Table 5).

Of the 55 Tc-99m MIBI parathyroid SPECT studies, 20 were positive for parathyroid adenoma. Only 1 patient had a coexisting pituitary adenoma and a parathyroid adenoma. Genetic examinations revealed Q405X heterozygote for Multiple Endocine Neoplasia Type I (MEN I). He also had a family history of MEN I. Because there was only one patient with MEN I, no comparison analysis such as MEN versus non-MEN could be done.

Discussion

Tc-99m MIBI is a well-known tumor-imaging agent. Parathyroid tumors are one of the most common indications for tumor imaging by Tc-99m MIBI.[5] Cranium is involved in region of interest in parathyroid SPECT studies. Incidental Tc-99m MIBI uptake was observed in some of the patients with hyperparathyroidism who were referred to Nuclear Medicine Department for parathyroid SPECT imaging. Incidental Tc-99m MIBI uptake in pituitary adenomas has been reported before,[6–8] but the literature was found lacking enough of enlightening information for the clinical importance of pituitary Tc-99m MIBI uptake and possible factors affecting degree of this uptake. The authors aimed to investigate if there were any factors affecting incidental pituitary uptake of Tc-99m MIBI and to define a quantitative

Table 4. Comparison of the P/C Values Between the Patients Who Have an Adenoma with Regular Borders and Homogenous Content and the Subjects with Tumors Including a Cystic Necrotic Component or Invasion

Additional radiological features of the tumor	*No additional findings on MRI* (n = *14*)	*Any additional finding on MRI* (n = *10*)	p
Age	51 (42.5–57.5)	58 (39.8–62.0)	0.585
P/C	30.3 (21.2–51.8)	29.0 (19.8–55.6)	0.546

Table 5. Comparison Results of Age, P/C, MRI Highest Dimension and MRI Calculated Volume Values for the Patients Who Received No Treatment and the Subjects Who Had Undergone Any Treatment

	No treatment (n = 13)	*Any treatment (n = 11)*	p
Age	56 (44.5–60.5)	49 (40.0–59.0)	0.494
P/C	35.3 (23.4–61.8)	22.5 (19.7–52.8)	0.228
MRI highestdimension	10.0 (3.5–13.5)	12 (6–25)	0.186
MRI volume	251 (33–567)	490 (56–5962)	0.228

index in Tc-99m MIBI SPECT studies for indicating pituitary tumors.

In the study, a total of 55 patients were enrolled. Study group included 24 patients who had a pituitary adenoma. Control group consisted of 31 patients who had no signs of a pituitary adenoma. The two groups were statistically similar in terms of gender, but not of age.

Median P/C rates were found to be distinctively higher in the study group compared with the control group. This finding was compatible with the results of other studies investigating incidental pituitary Tc-99m MIBI uptake.[6,7] Tiktinsky et al. have retrospectively evaluated 56 consecutive Tc-99m MIBI SPECT studies, but radiological data (CT or MRI) for confirmation of the nature of the pituitary uptake could be obtained in 18 patients and only 4 of them had a pituitary pathology. As the authors already mentioned, the study population was small for certain statements about pituitary MIBI uptake.[6] In the study, the authors enrolled 24 patients in the study group and 31 patients in the control group, so that the groups were more balanced, and they could make a more precise statistical evaluation. Furthermore, they had MRI results of each patient in both groups, confirming an adenoma or a normal pituitary gland. CT data were not taken under consideration to avoid heterogeinity. They carried out a ROC analysis to find a possible cutoff value for P/C with highest sensitivity and specificity. The results were highly significant as for value of 7.675, sensitivity, specificity, positive predictive value, and negative predictive value were found to be 100%, 96.8%, 96%, and 100%, respectively. Thus, levels above 7.675 for P/C should be mentioned in parathyroid SPECT reports as a suspicious finding for a coexisting pituitary adenoma and further clinical and/or radiological investigations may be indicated.

Previous studies revealed similar results for Tc-99m MIBI uptake in pituitary adenomas.[6–8] However, factors contributing to the density of this uptake have not been investigated before. In this study, the authors analyzed several possible factors, such as the biochemical nature of the adenoma, the treatments received, size of the tumor, other additional characteristics of the tumor-like local invasion, or cystic necrotic component. Although the number of patients is small, nonparametric statistical tests showed that there was no correlation between investigated factors and degree of pituitary Tc-99m MIBI uptake.

There were three types of tumors among the patients in this study: nonfunctioning adenomas, prolactin, or growth hormone secreting adenomas. In this study, the authors could only make a general comparison for uptake levels of Tc-99m MIBI between biochemically functioning and nonfunctioning pituitary adenomas because all three groups included small number of subjects. Correlation analysis showed that there was no significant difference between functioning and nonfunctioning groups. The uptake mechanism for Tc-99m MIBI in tumoral tissue is thought to be mitochondrial uptake by means of the cathionic charge of the molecule and number of mitochondria is known to be variable in both functioning and nonfunctioning pituitary tumors. Only the ones with an oncocytic change in somatomammotroph adenomas and nonfunctioning oncocytic adenomas show mitochondrial accumulation.[9,10] Thus, it is not a surprising finding that Tc-99m MIBI uptake is also variable among these groups. Kunishio et al. also reported similar results before.[8]

Tc-99m MIBI SPECT applications in other childhood and adult brain tumors have been reported earlier. This method is known to be complementary to radiological imaging (CT, MRI) in preoperative evaluation, evaluation of chemotherapy and/or radiotherapy response, and determination of viable residual tumor tissue following therapies. In a previous study, it has been reported that pituitary Tc-99m MIBI uptake was markedly lower in patients who received any treatment with respect to the patients who have been newly diagnosed. In the study, one may expect to find a similar difference between uptake degrees of Tc-99m MIBI in patients who received any treatment and the ones who received none. But the heterogeneity of the treatments received together with the variability in the functional classification of the pituitary tumor, may be responsible from insignificant results in comparative statistics.[4,11,12]

In previous brain SPECT studies, tumor/background ratios were found to be highly correlated with the size or volume of the tumors.[11,12] In this study, they found no such significant correlation for the whole study group. However, this was true for tumors less than 1 cm in highest diameter. Partial volume effect is a well known entity causing a misdiagnosis of small lesions. Activities smaller than twice as large as the full width at half maximum (FWHM) of the system is said to be indistinguishable from background activity. Although FWHM was 8 mm for the gamma camera system, they could still differentiate microadenomas. This finding agrees well with the previous study of Kojima et al.[7] This result probably arises from the fact that principally very small lesions can be anyhow detected by SPECT as long as the lesion/background ratio is high enough.[13]

Fourteen of the subjects in the study group presenteed with a homogenous nodular lesion with regular borders on MRI scan. Ten of 24 patients, however, demonstrated either local invasion or had a cystic and/or necrotic and/hemorrhagic component. Patients with a local invasive tumor were expected to have a higher Tc-99m MIBI uptake considering previous studies, which demonsrated higher uptake values of this radiopharmaceutical in tumors of various organs with an aggressive behavior. On the contrary, necrosis or cystic components could be responsible for less radiopharmaceutical uptake.[14,15] This hypothesis could not be supported, however, with a statistical analysis, due to very small number of patients in each subgroup. A comparison between the tumors with no extra characteristics defined on MRI and the tumors with invasion or cystic and/or necrotic component showed no significant difference, as could be theoretically predicted.

The major limitation in this study was that only a small group of pituitary adenoma patients could be included in the study.

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Subgroups derived from these subjects were also very small to analyze. The major aim of this study was to investigate clinical significance of incidental Tc-99m MIBI uptake on parathyroid SPECT studies. By retrospective scanning of the registry, uptake patterns of the patients with pituitary adenoma and healthy subjects were compared. The study would contribute to the literature more powerfully if radiological correlation could be made in subjects with incidental pituitary uptake, prospectively. The calculated cutoff value would then be proved to be more reliable. However, referring these asymptomatic patients with no signs of a pituitary mass to MRI would also be doubtful for ethical reasons. In this study, several factors affecting Tc-99m MIBI uptake were investigated, but there may have been some other unevaluated conditions such as p-glycoprotein (pgp) or multidrug resistance-associated protein expression. Pgp expression, for example, has been reported to be responsible for Tc-99m MIBI washout from pituitary tumors.[8] In their study population, estimated uptake levels may not have been reached in adenoma patients due to some other molecular characteristics of the adenoma that were out of the scope of the study.

Conclusion

As a conclusion, incidental pituitary Tc-99m MIBI uptake on parathyroid SPECT studies may be noteworthy for a silent pituitary adenoma. Values above 7.675 for sellar region activity/cortical activity are especially suspicious for pituitary adenoma and can be mentioned as an incidental finding in parathyroid SPECT reports so that further clinical and radiological investigations can be made. Although there is a very significant difference between pituitary uptake levels of the study and control groups, Tc-99m MIBI uptake is not affected from the biochemical nature of the adenoma, the therapies received, size of the tumor, other additional characteristics of the tumor-like local invasion, or cystic necrotic component. Thus, occupying space in the sellar region may be an enough criterion for pituitary Tc-99m MIBI uptake. Subgroup analyses may still be misleading, and studies with larger patient groups are needed to support conclusions.

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Disclosure Statement

No competing financial interests exist.

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