Article

Effectiveness of ^{131}I nor-cholesterol Uptake per Unit Volume of Adrenal Adenoma in the Diagnosis of Aldosteronoma

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Diagnosis of adrenal adenomas for patients with primary aldosteronism is sometimes difficult only by referring to the visualization pattern in adrenocortical scintigraphy without regards to standard scintigraphy or suppression scintigraphy with dexamethasone. We studied if quantitative evaluation of the standard scintigraphy without dexamethasone suppression can be useful to diagnose aldosteronomas. Twenty-nine patients who had undergone adrenalectomy with different clinical manifestations (16 patients with primary aldosteronism, 6 patients with Cushing's syndrome and 7 patients without hormonal abnormality) were included in the study. Volume of the adrenocortical adenomas, ^{131}I nor-cholesterol uptake of the adrenocortical adenomas, and ^{131}I nor-cholesterol uptake per unit volume of the adrenocortical adenomas were compared between the 3 groups. The volume of adrenocortical adenomas in the patients with primary aldosteronism was significantly lower than those in the other two groups (Cushing's syndrome $p < 0.01$, Non-hormonal abnormality $p < 0.01$). No significant differences were found between the 3 groups in terms of ^{131}I nor-cholesterol uptake of adrenocortical adenoma. The ^{131}I nor-cholesterol uptake per unit volume of adrenocortical adenomas was significantly higher in the patients with primary aldosteronism than those in the other two groups (Cushing's syndrome $p < 0.001$, Non-hormonal abnormality $p < 0.001$). ^{131}I nor-cholesterol uptake per unit volume of adenoma obtained from adrenocortical scintigraphy without dexamethasone suppression can be useful in the diagnosis of aldosteronoma.

Key Words : ^{131}I nor-cholesterol, uptake per unit volume, adrenal adenoma, diagnosis, aldosteronoma

1. Introduction

In clinical settings we sometimes observe adrenocortical adenomas on ultra-sonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). They might be found incidentally during health checks or found in detailed examinations to identify primary focus causing hormonal abnormalities with symptoms such as hypertension, hyperlipidemia and diabetes mellitus.

In each imaging modality, several key points are known to diagnose adrenal lesions as

adrenocortical adenomas. Adrenocortical adenomas are likely to have low attenuation at nonenhanced CT and show washouts greater than 50% of contrast material on a 10-minute delayed CT scan^(1,2). Their lipid contents can be detected by comparing between in-phase and out-of-phase MR chemical-shift images⁽³⁾. ^{131}I nor-cholesterol studies of adrenocortical adenomas show significantly increased uptake and can differentiate adrenocortical adenomas from malignant adrenal masses^{(4)–(6)}. However, the above-mentioned reports only indicate that adrenal lesions are adrenocortical adenomas, but

can neither tell us whether they are hormonally active nor distinguish adenomas with primary aldosteronism from those with Cushing's syndrome. Adrenal venous sampling (AVS) has been reported to be useful to identify aldosterone-producing adenomas^{7),8)}. However, AVS is an invasive method and the success rate depends on the proficiency of the angiographer⁹⁾.

Adrenocortical scintigraphy using ¹³¹I nor-cholesterol has been used to evaluate the functional status of adrenocortical tissue when other imaging studies like CT and MRI are indeterminate. Typical visualization patterns of unilateral adrenal adenomas are known to be unilateral strong adrenal visualization for Cushing's syndrome, warm spot with overlaying normal adrenal visualization for primary aldosteronism and can be similar to the patterns of Cushing's syndrome or to those of primary aldosteronism for adenomas without hormonal abnormality.

Fukunaga et al. suggested the usefulness of adrenocortical scintigraphy with dexamethasone suppression for localizing and differential diagnosis for the patients with primary aldosteronism¹⁰⁾. However, some reports indicate that in primary aldosteronism adrenal scintigraphy is hampered by a relatively high incorrect classification between unilateral adenoma and bilateral idiopathic hyperplasia, regardless of whether standard scintigraphy or suppression scintigraphy with dexamethasone were performed^{11),12)}. We have very few reports stressing the quantitative evaluation of ¹³¹I nor-cholesterol adrenocortical uptake for the diagnosis of adrenal adenomas for patients with primary aldosteronism.

Our purpose of the study is to see if the quantitative evaluation of ¹³¹I nor-cholesterol

adrenocortical uptake without dexamethasone suppression could be useful for the diagnosis of aldosteronomas.

2. Methods

Twenty-nine patients in whom unilateral adrenal masses had been identified by imaging modalities and who had undergone adrenalectomies from August 1999 to June 2009 were retrospectively included for the analysis. These 29 patients were 10 males and 19 females, with an age range of 31 to 71 years (mean age, 52.8 years) for male patients and an age range of 27 to 71 years (mean age, 50.4 years) for female patients. The patients consisted of 16 patients with primary aldosteronism, 6 with Cushing's syndrome and 7 with non-hormonal abnormalities. Hormonal values were determined by radioimmunoassay or immunoradiometric assay methods using commercially available kits. Adrenal function was considered normal when the corresponding hormone values were in the normal range. Conversely, cortical adrenal hypersecretion was defined in cases of clearly increased levels of the corresponding hormones. Before ¹³¹I nor-cholesterol injection, thyroid iodine uptake was blocked with a saturated solution of potassium iodide (200 mg·day orally, starting the day before tracer administration and continuing for 7 days). The patients received intravenous injection of 37 MBq of ¹³¹I nor-cholesterol and one week after the injection, they were imaged with a two-headed camera (GCA-7200A/DI, Toshiba, Tokyo) equipped with middle-energy collimators and set at a 364 keV peak with a 20% window. The adrenocortical uptake without absorption correction was calculated. Dexamethasone suppression was not applied to any patient in the imaging studies.

The method for the calculation of adrenal uptake was based on images of the adrenal and syringe counts before and after radiopharmaceutical injection. The number of counts present in the adrenal (AD) was determined by a manually determined region of interest (ROI) drawn around the borders of the adrenal on the posterior view. Another square ROI was drawn by the same process beside the adrenal for background subtraction (BG). The radioactivity in the syringe before (B) and after (A) radiopharmaceutical injection was obtained from a dose calibrator (Aloka, Curiemeter IGC-7, Tokyo, Japan). The adrenal uptake (U%) was calculated according to the following equation.

$$U = \text{Cf} \cdot (\text{AD} - \text{BG}) \times 100 / (\text{B} - \text{A})$$

Cf in the above equation is a calibration factor to compensate the difference of detection efficiency between the dose calibrator and scintillation camera and was calculated according to the following equation.

$$\text{Cf} = \text{Vdc} / \text{Vsc}$$

Where Vdc is the remaining radioactivity in the vial after radiopharmaceutical injection on the day of radiopharmaceutical injection and Vsc is the number of counts present in a square ROI containing the borders of the vial on the planar view imaged on the same day for the adrenocortical imaging and back ground subtraction was performed by the same procedure as in the adrenocortical imaging.

The shape of each adrenocortical adenoma was approximated as a spheroid and the volume was calculated by the following formula applicable to spheroid.

$$\text{Volume} = \pi abc / 6$$

Where a, b and c are the lengths of major axes of each spheroid.

For application of the above formula, we used the measured lengths of major axes on the pathological reports. The volume, the ^{131}I nor-cholesterol uptake, and the ^{131}I nor-cholesterol uptake per unit volume of the adrenocortical adenomas were compared between the 3 groups of primary aldosteronism, Cushing's syndrome and non-hormonal abnormality.

Statistical analysis was conducted using Stat-Mate III PC software (ATM, Tokyo, Japan) for Kruskal-Wallis test with Dunn's posttest and Pearson's correlation coefficient test. Statistical significance was set at $p < 0.05$.

3. Results

The volume of adrenocortical adenomas was significantly lower in the primary aldosteronism group than those in the other two groups (Cushing's syndrome $p < 0.01$, non-hormonal abnormality $p < 0.01$) (Fig. 1). No significant differences were found between the 3 groups

Fig. 1 Comparison of volume of adrenocortical adenomas between the three groups.

Fig. 2 Comparison of ^{131}I nor-cholesterol uptake of adrenocortical adenomas between the three groups.

Fig. 3 Comparison of ^{131}I nor-cholesterol uptake per unit volume of adrenocortical adenomas between the three groups.

in terms of ^{131}I nor-cholesterol uptake of adrenocortical adenoma (Fig. 2). The ^{131}I nor-cholesterol uptake per unit volume of adrenocortical adenomas was significantly higher in the primary aldosteronism group than in the other two groups (Cushing's syndrome $p<0.001$, non-hormonal abnormality $p<0.001$) (Fig. 3). Se-

rum aldosterone values obtained within one month before adrenocortical scintigraphy were available in the study and used for correlation analysis with the ^{131}I nor-cholesterol uptake of aldosteronomas in 11 patients. There was a good positive correlation between the serum aldosterone values and the ^{131}I nor-cholesterol uptake in adenomas of the patients with primary aldosteronism ($r=0.6275$, $p<0.05$) (Fig. 4).

4. Discussion

4.1 Study results

Our purpose of the study was to evaluate the possibility of diagnosing aldosteronomas quantitatively by referring to the volume and the ^{131}I nor-cholesterol uptake of the adrenocortical adenomas obtained in the adrenocortical imaging without dexamethasone suppression. Aldosteronomas are known to be typically small (around 1 cm^3 in volume), which was reconfirmed in our study. Although the uptake itself was shown not to be useful for differentiation between the three kinds of adrenocortical adenomas, there was a good correlation between the serum aldosterone values and the ^{131}I nor-cholesterol uptake in aldosteronomas. Similar result showing a significant correlation between urinary aldosterone excretion and ^{131}I nor-

cholesterol uptake in aldosteronomas was reported by Gross et al¹³⁾. Our study showed that the uptake per unit volume of adrenocortical adenoma could be used to differentiate patients with primary aldosteronism from the patients with Cushing's syndrome and also from the patients with non-hypersecreting adrenocorti-

Fig. 4 Correlation between serum aldosterone values and uptake of ^{131}I nor-cholesterol in adenomas for patients with primary aldosteronism ($n = 11$).

cal adenoma. We can calculate ^{131}I nor-cholesterol uptake per unit volume for an adrenocortical adenoma preoperatively by referring to the uptake from adrenocortical scintigraphy and can estimate volume of adrenal adenomas from imaging modalities such as CT and MRI. The estimated ^{131}I nor-cholesterol uptake per unit volume could be useful for the diagnosis of aldosteronomas.

Demand for the ability to diagnose aldosteronomas correctly is increasing because primary aldosteronism has been reported as being far more common than previously believed among hypertensive patients¹⁴. Imaging modalities such as US, CT and MRI have not been able to respond adequately to the demand. AVS is one of the solutions, however, it is invasive and the success rate to define aldosteronomas correctly depends too much on angiographers' proficiencies and AVS interpretation rules to be the gold standard¹⁵. Compared with AVS, scintigraphic methods are target-specific, non-invasive and unnecessary to worry about interpreters' proficiencies. A PET tracer for adrenocortical imaging, ^{11}C metomidate, has been shown to be useful to differentiate cortical tumors from non-cortical tumors^{16, 17}. Hennings

et al showed that mean standardized uptake value (SUV) in a ^{11}C metomidate PET study was higher in aldosteronomas (mean SUV : 30.7) than in cortisol secreting adenomas (mean SUV : 20.3) and also in nonfunctional adenomas (mean SUV : 18.4)¹⁸. Although statistical significance of higher SUV in aldosteronomas was not confirmed in their report, their result is consistent with our result showing higher ^{131}I nor-cholesterol uptake per unit volume in aldosteronomas.

4.2 Study Limitations

Because the aldosteronomas are small and it is sometimes difficult to separate the adenoma from the adjacent adrenal tissue in activity especially in small ones (less than 1 cm in diameter) during the process of setting an ROI over the adenoma-bearing adrenal gland on the posterior view, overestimation of uptake is likely to occur. From the experience of adrenocortical scintigraphy studies without dexamethasone suppression in our hospital, the mean uptake for normal adrenal tissue is around 1%. The range of the uptake for the 16 aldosteronomas in the study is 4 to 75%. These values lead us to probable overestimation of the uptake ranging 1 to 33%.

Although microadenomas (less than around 4 mm in diameter) can sometimes cause primary aldosteronism, they are very difficult to detect in conventional adrenocortical scintigraphy using ^{131}I nor-cholesterol as well as in CT and MRI with slice thickness of 5 mm to 7 mm. PET/CT (PET using radiopharmaceutical tracers like ^{11}C metomidate and CT with thinner slices) might be useful to detect microadenomas causing primary aldosteronism.

The number of patients included in our study is small. Further studies with much larger number of cases will be needed to assure the utility of quantitative adrenocortical scintigraphy study.

5. Conclusion

¹³¹I nor-cholesterol uptake per unit volume of adenoma obtained from adrenocortical scintigraphy without dexamethasone suppression can be useful in the diagnosis of aldosteronoma.

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要 旨

アルドステロノーマの診断における副腎腺腫単位体積あたりの ^{131}I アドステロール集積率の有効性

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原発性アルドステロン症の原因となる副腎腺腫の診断は、副腎 ^{131}I アドステロールシンチグラフィでの左右副腎の描出パターンのみからでは、通常のシンチグラフィあるいはデキサメサゾン抑制副腎シンチグラフィにおいても難しい場合がある。通常のデキサメサゾン非抑制副腎シンチグラフィを定量的に評価し、アルドステロノーマの診断が可能であるかを検討した。片側副腎腺腫摘出術前にデキサメサゾン非抑制副腎シンチグラフィを行った原発性アルドステロン症 16 名、クッシング症候群 6 名、非症候性 7 名の 3 グループ計 29 名の患者を対象とした。摘出副腎腺腫の体積、 ^{131}I アドステロールシンチグラフィでの集積率、副腎腺腫単位体積あたりの ^{131}I アドステロール集積率を 3 群間で比較した。副腎腺腫の体積は原発性アルドステロン症において他の 2 群より有意に小さかった (クッシング症候群 $p < 0.01$, 非症候性 $p < 0.01$)。集積率に 3 群間で有意差はみられなかったが、単位体積あたりの集積率は原発性アルドステロン症において他の 2 群より有意に大きかった (クッシング症候群 $p < 0.001$, 非症候性 $p < 0.001$)。通常のデキサメサゾン非抑制副腎シンチグラフィから得られる単位体積あたりの ^{131}I アドステロール集積率は、原発性アルドステロン症をクッシング症候群や非機能亢進性副腎腺腫と鑑別する上で有用であると思われる。