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ORIGINAL ARTICLE

Use of NP-59 (^{131}I-iodocholesterol) Scan as a Potential Alternative to Adrenal Venous Sampling in the Investigation of Primary Aldosteronism: a 5-Year Retrospective Study

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ABSTRACT

Objectives: *To evaluate the usefulness of NP-59 (^{131}I-iodocholesterol) scan as a non-invasive alternative to adrenal venous sampling in the diagnosis of Conn's syndrome and lateralisation of aldosterone production.*

Methods: *The electronic patient records of 39 consecutive patients who were referred for NP-59 scan in our centre between 1 January 2007 and 31 December 2012 were reviewed. The results of NP-59 scan, biochemical test, subsequent treatment plan, histopathology findings, and clinical outcome were evaluated.*

Results: *Of the 39 patients, 17 had successful lateralisation of aldosterone production by NP-59 scan. Of these 17 patients, 11 had unilateral adrenalectomy, six patients refused surgery. Unilateral adrenalectomy treatment success was reported in all 11 (100%) patients who had lateralisation of aldosterone source by NP-59 scan.*

Conclusion: *Our study has shown that NP-59 scan as a single imaging investigation has excellent positive predictive value in the diagnosis of aldosterone-producing adenoma (Conn's syndrome) and NP-59 scan can be used as an alternative to adrenal venous sampling.*

Key Words: *Adosterol; Adrenocortical adenoma; Hyperaldosteronism; Hypertension; Radionuclide imaging*

中文摘要

NP-59（^{131}I-iodocholesterol）掃描替代腎上腺靜脈採血診斷原發性醛固酮增多症：五年回顧性研究

陳可鋒、鄭力暉

目的：探討NP-59（^{131}I-iodocholesterol）掃描作為替代腎上腺靜脈採血的一種非侵入性工具，用於診斷康氏症（Conn's syndrome）和醛固酮偏側分泌的有效性。

方法：回顧於2007年1月1日至2012年12月31日期間轉介至本中心進行NP-59掃描的連續39例病人的電子病歷。評估NP-59掃描結果、生化檢驗、隨後的治療計劃、組織病理學結果和臨床結果。

結果：39名患者中，NP-59掃描成功檢測單側醛固酮分泌17例。這17名患者中，11人接受單側腎上腺切除術，餘下6人拒絕接受手術。11例NP-59掃描檢測到單側醛固酮分泌源的病人的單側腎上腺切除術治療成功率達至100%。

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結論：本研究顯示NP-59掃描作為一種單獨的影像檢查，其診斷醛固酮分泌腺瘤（康氏症）具有極佳陽性預測值。此外，NP-59掃描可用作腎上腺靜脈血採樣的替代檢查。

INTRODUCTION

Primary aldosteronism is defined as the inappropriate, autonomous hypersecretion of aldosterone in the absence of activation of the renin-angiotensin-aldosterone axis.[1] It is the most common form of secondary hypertension and is estimated to be responsible for 5% to 20% of all cases of hypertension.[2] Aldosterone is a mineralocorticoid hormone produced by the zona glomerulosa, the outermost cortical zone of the adrenal gland and was first described by Garrod et al in 1956.[3] The first case of primary aldosteronism was described by Conn in 1955.[4] Primary aldosteronism has two main causes, namely aldosterone-producing adenoma (APA, also known as Conn's syndrome) and bilateral adrenal hyperplasia (BAH).[1,2,5] It is important to differentiate the two since Conn's syndrome is generally managed by unilateral adrenalectomy which is potentially curative, while BAH is managed medically.[1,2,5]

Adrenal venous sampling (AVS) is considered the standard of reference for determining the cause of primary aldosteronism.[1,6-8] However, AVS is technically demanding, in particular, cannulation of the right adrenal vein which directly drains into inferior vena cava.[1,6-8] The reported success rate varies significantly among different centres.[6,7]

The NP-59 scan has been used for imaging of the adrenal cortex since 1975.[9,10] NP-59 circulates in the bloodstream and binds to low-density lipoprotein receptors in the adrenal cortex.[1,9-11] The technique allows non-invasive assessment of adrenal function and can be used to differentiate between APA and BAH. Administration of dexamethasone, which suppresses adrenal cortical hormones, markedly improves the diagnostic accuracy of adrenal scintigraphy.[12,13] Unilateral adrenal uptake on NP-59 scintigraphy most likely indicates APA, and bilateral symmetrical uptake suggests BAH.[11,14-17]

The aim of this study was to evaluate the usefulness of NP-59 (^{131}I-iodocholesterol) scan as a non-invasive alternative to AVS in the diagnosis of Conn's syndrome and lateralisation of aldosterone production. This study was conducted in a nuclear medicine centre, which receives referrals from an affiliated hospital providing endocrinology service but with limited interventional radiology support.

METHODS

Subjects

The electronic patient records (ePRs) of patients who were referred for NP-59 scan to our centre between 1 January 2007 and 31 December 2012 were reviewed. All of them had biochemically confirmed primary aldosteronism. A total of 39 consecutive patients were recruited. The scintigraphic images, reports, and clinical notes were reviewed through Picture Archiving and Communication System and ePR. The result of NP-59 scan, biochemical tests, subsequent treatment plan, histopathology findings, and clinical outcomes were evaluated.

Patient Preparation and Scintigraphy Technique

Dexamethasone suppression regimen of 1 mg orally 4 times daily was started 7 days before and continued for 5 days after the day of NP-59 injection. Dexamethasone helps suppress NP-59 uptake by the adrenocorticotrophic hormone–dependent, glucocorticoid-producing part of adrenal cortex, preventing the masking of uptake by the zona glomerulosa of the adrenal cortex, which is responsible for aldosterone production. Lugol's iodine solution 1 ml daily was prescribed for 8 days starting 1 day before injection. Lugol's solution protects the thyroid by blocking thyroid uptake of free iodine-131 resulting from in-vivo deiodination of NP-59 agent.

Scintigraphic images were acquired with ADAC Vertex Gamma camera (Philips; Amsterdam, Netherland). Planar NP-59 images of adrenal glands — including anterior and posterior views — were taken on day 3, day 4, day 5, and day 7 with centre at the upper border of kidneys for 1200 seconds. Single-photon emission computed tomography (SPECT) images of upper abdomen were acquired on day 4 with the same range.

Image Interpretation

Scintigraphic images were interpreted by fully qualified nuclear medicine or radiology specialists who were experienced in adrenal cortical imaging. Successful

lateralisation is defined as early visualisation of tracer uptake on either side and asymmetrical uptake in subsequent delayed imaging.

Clinical Outcome

All patients were followed up in the endocrinology specialist outpatient clinic. Adrenalectomy treatment success was defined as normalisation of hypokalaemia without potassium supplement, plus either step-down of antihypertensive regimen or cure of hypertension in subsequent clinical follow-up.

RESULTS

Scintigraphic Results

Successful lateralisation of aldosterone production by NP-59 scan was reported in 17 of the 39 cases. Examples of positive and negatives scans are illustrated in Figure 1 and Figure 2, respectively. Of these 17 patients, 11 had unilateral adrenalectomy, six refused surgery. Patient characteristics, scintigraphic findings,

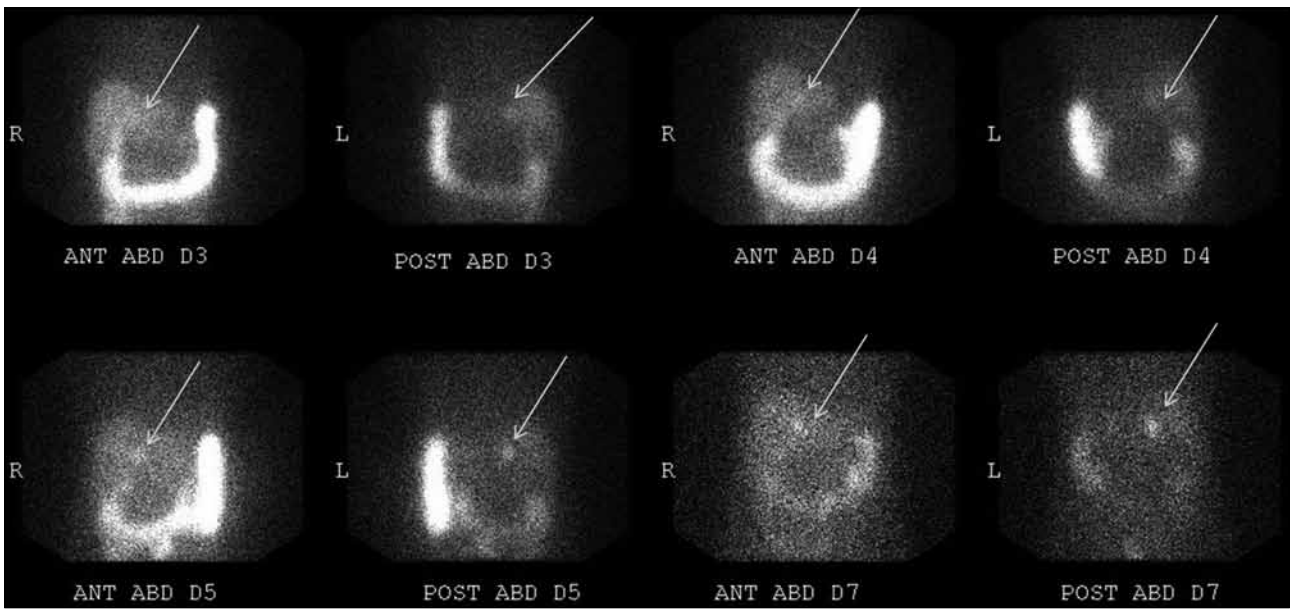

Figure 1. Positive scans of lateralisation of aldosterone production. Early visualisation on day 3 and marked asymmetrical uptake is noted in the right adrenal gland (arrows). The intense tracer activity in colon is physiological.

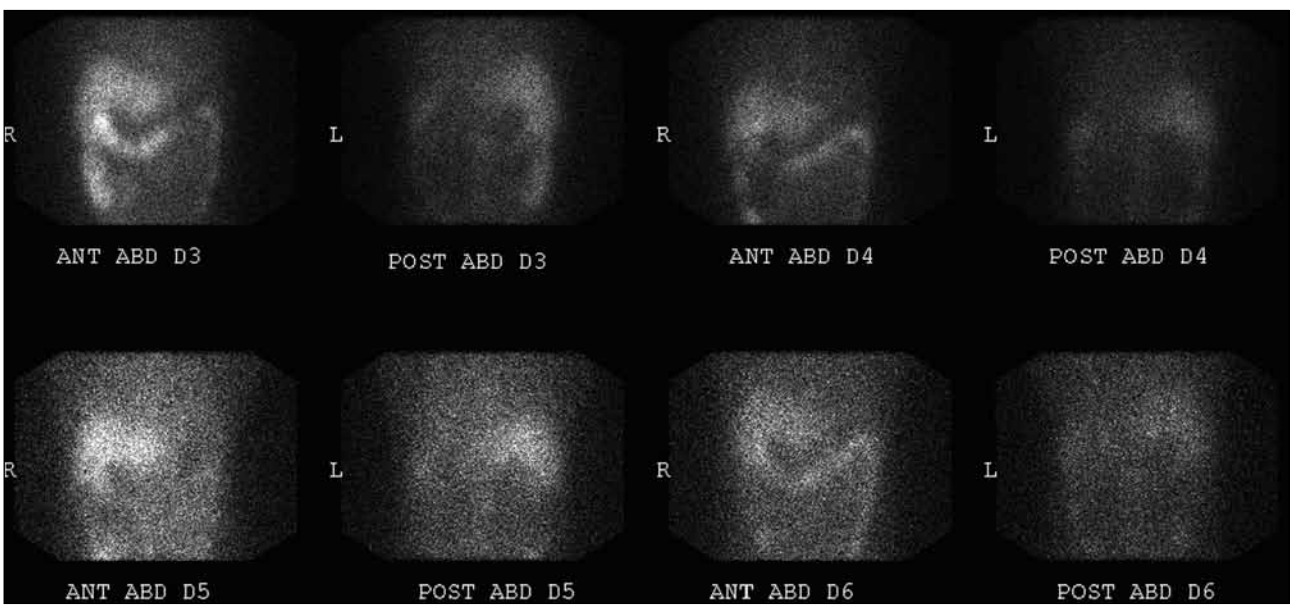

Figure 2. Negative scans of lateralisation of aldosterone production. No asymmetrical uptake is noted in either adrenal gland.

pathology, and treatment outcomes are summarised in the Table.

Histopathological Correlation

Conn's tumour was confirmed by histopathology in 10 (91%) of the 11 patients who had unilateral adrenalectomy; adrenal hyperplasia was reported in one case. This patient reported normalisation of hypokalaemia and improvement of blood pressure, which suggested that this patient was likely to have unilateral hyperplasia.

Unilateral Adrenalectomy Outcome

Unilateral adrenalectomy treatment success was reported in all 11 (100%) patients who had lateralisation of aldosterone source by NP-59 scan.

NP-59 scan failed to lateralise the source of aldosterone in 22 patients. According to ePR, AVS was performed in two of these patients but was unsuccessful. Medical treatment was continued in these 22 patients.

DISCUSSION

Selecting patients who have APA (Conn's syndrome) among primary aldosteronism patients is of utmost importance since these patients are curable by unilateral adrenalectomy.[1,2,5,8] On the other hand, surgical procedure has to be avoided in patients who have BAH, which should be managed with medical therapy.[8]

Our study has shown that the NP-59 scan as a single imaging investigation has excellent positive predictive value in the diagnosis of APA. The excellent positive predictive value of NP-59 scan has been suggested by a few published studies.[16-21] However, in most of these studies, NP-59 was investigated as an adjunct imaging tool when AVS or other non-invasive imaging modalities were inconclusive, rather than as a single investigation, as in our study.

More importantly, all our patients who had lateralisation of aldosterone source by NP-59 scan reported treatment success after adrenalectomy. Therefore, we can conclude that lateralisation by NP-59 scan is a reliable predictor of successful adrenalectomy outcome and NP-59 is useful in identifying surgical candidates among primary aldosteronism patients.

Nevertheless, this study had limitations. First, it was a retrospective study. Second, the pathology results of patients who were not operated on were not known and, therefore, the false-negative rate of NP-59 scan cannot be evaluated. In other words, the sensitivity and specificity of NP-59 could not be calculated.

It is interesting to note that the pathology of one of the adrenalectomies was adrenal hyperplasia. This patient reported normalisation of hypokalaemia and blood pressure after adrenalectomy, which suggested that this was likely a case of unilateral hyperplasia. Unilateral adrenal hyperplasia was first recognised by Ross in 1965.[22] Since then, there have been at least 156 published cases in the English literature and the actual prevalence is believed by some investigators to be higher than that was published.[23-28] Most of the literature suggests that APA and unilateral hyperplasia cannot be differentiated before surgery.[23-28] However, from a practical point of view, it may not be necessary to differentiate the two because both conditions can benefit from unilateral adrenalectomy.

Table. Summary of the characteristics, scintigraphic findings, pathology, and treatment outcomes of patients who underwent adrenalectomy.

Patient No.	Age (years)	Sex	NP-59 scintigraphic findings	Pathology	Outcome
1	42	F	Right-sided lateralisation	Adrenal cortical adenoma	Normalisation of blood pressure of hypokalaemia
2	53	F	Right-sided lateralisation	Adrenal cortical adenoma	Improvement of hypertension and normalisation of hypokalaemia
3	52	F	Right-sided lateralisation	Adrenal cortical adenoma	Normalisation of blood pressure of hypokalaemia
4	60	F	Right-sided lateralisation	Adrenal cortical adenoma	Improvement of hypertension and normalisation of hypokalaemia
5	56	M	Right-sided lateralisation	Adrenal cortical adenoma	Improvement of hypertension and normalisation of hypokalaemia
6	64	M	Left-sided lateralisation	Nodular hyperplasia	Improvement of hypertension and normalisation of hypokalaemia
7	54	F	Right-sided lateralisation	Adrenal cortical adenoma	Normalisation of blood pressure of hypokalaemia
8	48	F	Left-sided lateralisation	Adrenal cortical adenoma	Normalisation of blood pressure of hypokalaemia
9	69	F	Right-sided lateralisation	Adrenal cortical adenoma	Normalisation of blood pressure of hypokalaemia
10	57	M	Right-sided lateralisation	Adrenal cortical adenoma	Improvement of hypertension and normalisation of hypokalaemia
11	57	F	Left-sided lateralisation	Adrenal cortical adenoma	Normalisation of blood pressure of hypokalaemia

It has been proposed that patients with biochemically confirmed primary aldosteronism should have cross-sectional imaging such as computed tomography (CT) or magnetic resonance imaging first. If the result is equivocal, further investigation with AVS or NP-59 scintigraphy can be performed.[1] AVS is considered the gold standard in determining the causes of primary aldosteronism.[1,6,7,21] However, AVS is invasive and not without complications. Although the success rate in a few dedicated centres can reach >90%, the reported success rates among other centres are highly variable.[6-8,21] In 2011, Vonend et al[7] reported that the success rate of AVS was between 8% and 61%. Moreover, interventional radiology service may not be available in every hospital treating primary aldosterone patients. Given its high positive predictive value and non-invasiveness, NP-59 scan can be used as an alternative to AVS in cases with equivocal cross-sectional imaging findings, especially in centres lacking interventional radiology expertise. The scintigraphic scans in our study were performed without hybrid SPECT/CT. This imaging modality provides both functional and anatomical information. It helps distinguish gastrointestinal tract activity versus adrenal uptake. It also allows assessment of distribution of uptake within the adrenal gland and helps differentiate nodular hyperplasia from small adenoma.[15] It has been suggested that the SPECT/CT scan significantly improves the sensitivity of NP-59 scan and allows the detection of small sub-centimetre functioning adenomas. Also, routine use of SPECT/CT could simplify the NP-59 imaging procedure by requiring only a single imaging time-point on day 3 or 4.[11] In fact, we have installed a new SPECT/CT facility in our centre and further study with NP-59 SPECT/CT is under way.

CONCLUSION

In patients with primary aldosteronism and equivocal cross-sectional imaging, NP-59 (^{131}I-iodocholesterol) scan can be used as an alternative to AVS to lateralise source of aldosterone production, especially in hospitals with limited interventional radiology service.

DECLARATION

No conflicts of interests were declared by authors.

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