Is there a role for Nuclear Medicine in diagnosis and management of patients with primary aldosteronism?

Abstract

Primary aldosteronism (PA) is the most common cause of secondary hypertension. The diagnosis of PA is of clinical importance for choosing the appropriate treatment, meaning, surgery for the unilateral disease, and inclusion of aldosterone antagonists in the antihypertensive treatment for the bilateral disease. Current diagnostic approaches showed that the prevalence of PA is much higher than previously estimated. There is still controversy regarding the true prevalence of PA in hypertensive patients. The gold standard for differentiating between unilateral and bilateral disease is the adrenal vein sampling (AVS), a method that is invasive and is performed accurately in only few dedicated centers. Non invasive methods (imaging) for discriminating the two entities are: the CT scan, MRI and iodocholesterol (NP-59) scintigraphy performed under dexamethasone suppression. But the accuracy of imaging compared to AVS is suboptimal and can result in wrong therapeutic decisions. NP-59 scintigraphy is a non-invasive functional imaging technique that reveals the adrenal cortical autonomic function and could have of incremental value over anatomical imaging. *In conclusion,* in previous years NP-59 scintigraphy was used infrequently, but recently with the advent of hybrid single photon emission tomography (SPET/CT) systems the interest in NP-59 scintigraphy has been renewed. Studies comparing NP-59 SPET/CT imaging with AVS are warranted in order to establish its diagnostic accuracy.

Hell J Nucl Med 2013; 16(2): 134-139 *Published on line: 20 July 2013*

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Keywords: Primary aldosteronism - Iodocholesterol scintigraphy - NP-59 - SPET/CT

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Received:
14 May 2013
Accepted:
1 July 2013

Introduction

Conn in 1955 described for the first time a patient with an adrenal adenoma that produced aldosterone [1]. Primary aldosteronism (PA) is induced by autonomous overproduction of the salt-retaining hormone, aldosterone by the adrenal cortex, resulting in suppressed levels of renin and angiotensin II. Primary aldosteronism is considered the most common identifiable cause of secondary hypertension that is possibly amenable to surgical cure. The main characteristics of PA are hypertension, increased plasma aldosterone concentration (PAC) with reduced plasma renin activity (PRA), and hypokalemia which can be encountered in about 9%-37% of the cases. In subclinical PA, patients are often normokalemic and normotensive [2]. Other symptoms of PA may be fatigue, headache, muscle weakness, spams and numbness. There are three main clinical reasons for diagnosing PA. The first is that PA causes increased mortality and morbidity. Patients with PA have more often cardiovascular events such as arrhythmias, myocardial infarctions and strokes than matched controls with essential hypertension [3]. In a prospective study, patients with PA had a higher rate of 24h urine albumin excretion despite a normal glomerular filtration rate (GFR), compared to those with essential hypertension [4], while it has been reported that PA patients have worse quality of life [5]. It is supposed that the complications of PA result from mechanisms beyond the increase of blood pressure. The second reason is that mineralcorticoid receptor antagonists must be included in the therapeutic schedule of patients with PA, and the third, probably the most important, that patients with an aldosterone producing adenoma can be cured by surgical intervention.

Prevalence and biochemical diagnosis of PA

Primary aldosteronism was first reported to be present only in 1%-2% of the hypertensive population and the indication for its presence was mainly hypokalemia [2]. However, it is now acknowledged that hypokalemia is observed in more severe cases of PA. In the early 80's diagnosis of PA was accomplished by measuring PAC, PRA and their ra-

tio (aldosterone to renin ratio-ARR), that was introduced by Hiramatsu et al (1981) as a screening test [6]. With the use of ARR for screening purposes, the prevalence of PA increased significantly.

The measurements of PAC and PRA (or as the more recently introduced direct determination of plasma renin concentration) [7] can be influenced by many factors, resulting in a significant number of mostly false positive but also false negative results. Among these are medications (beta-adrenergic blockers, central a2 agonists, nonsteroidal anti-inflammatory drugs, diuretics, angiotensin-converting-enzyme inhibitors, angiotensine II receptor blockers, and renin inhibitors), and also potassium status, dietary sodium, advanced age, renal impairment, pregnancy, renovascular hypertension etc. Many different cut off points of ARR have been used for diagnosing PA. An ARR>20 with PAC ≥15ng/dL in the upright position has been considered compatible with the diagnosis of PA [8]. In screening patients with suspected PA using an ARR>40, with PRA levels not lower than 0.2ng/mL/h, some centers refer to 100% sensitivity, 84% specificity, 80% and 100% positive and negative predictive value, respectively. When increased ARR values indicate PA, confirmatory tests must be used like the oral sodium loading test, the fludrocortisone suppression test (considered as the gold standard), the saline infusion test and the captopril challenge test [9].

The frequency of PA among patients with refractory hypertension is reported to be within the range of 17% to 23% [10]. With the estimation that 7.5-15 million of Americans have resistant hypertension [11], a significant absolute number of patients may have PA. The frequency of PA in the general hypertensive population is lower. In a prospective study of 1125 hypertensive patients PA was found in 11.2% of the cases [12], while the Endocrine Society in 2008 reported PA to be present in 6.1%-10% of the hypertensive population [13]. Till now, the true prevalence of PA and its clinical importance are controversial [14]. There is also debate about the cost-effectiveness of screening all hypertensive patients for PA as well the cost effectiveness of the process for discriminating lateralization in order to identify patients for possible surgical treatment [15]. According to the Endocrine Society guidelines [13] searching for PA has to be focused on patients with hypertension stage>2, refractory hypertension, hypokalemia (spontaneous or diuretic-induced), adrenal incidentaloma, a family history of early onset hypertension, stroke occurring in patients younger than 40y, and in first degree hypertensive relatives of patients with PA.

Causes of PA

Once PA is verified, its cause should be identified. Primary aldosteronism can be induced by a) an aldosterone producing adenoma (APA) of the adrenal cortex (Conn syndrome), b) bilateral idiopathic micro/macro nodular hyperplasia (idiopathic hyperaldosteornism-IHA or bilateral adrenal hyperplasia-BAH), c) primary unilateral adrenal hyperplasia (PAH ή UAH) in less than 2% of cases, d) adrenocortical carcinoma in 1% of cases, e) familial hyperaldosteronism (FH-1 or glucorticoid-remediable aldosteronism-GRA) that is treated with glucorticosteroids, and f) some other extremely rare familial syndromes (FH-II, F-III). The most common causes of PA are APA and IHA. Different methods used for diagnosis also account for the different prevalence of APA and IHA in literature reports. The differentiation between these two entities is very critical for therapy selection, since surgical intervention is used mainly for APA but even for UHA [16]. Besides open surgical procedures, laparoscopic adrenalectomy is more frequently performed while newer techniques have emerged, like retroperitoneoscopic adrenalectomy, image-guided ablation [17], and robotic-assisted retroperitoneoscopic adrenalectomy [18]. Adrenalectomy restores hypokalemia and cures hypertension in about 50%-80%, while significant improvement is noticed in the rest of the patients who need less medication and have better blood pressure control [19]. In cases of bilateral disease medical treatment is indicated. In IHA, mineralocorticoid receptor antagonists are used, either spironolactone or the more specific eplerenone [20] and in GRA low doses of glucocorticosteroids.

Methods for discrimination of unilateral from bilateral PA

Differentiation between unilateral and bilateral disease is not an easy task. Biochemical tests, such as responsiveness of plasma aldosterone during upright position following overnight recumbency or during infusion of angiotensin II is encountered in most patients with IHA, but also in the angiotensin-responsive variety of APA which mimics IHA [21]. Imaging studies with computerized tomography (CT), magnetic resonance (MRI) and ^{131}I nor-cholesterol scintigraphy have been used for non-invasive differentiation of APA from IHA. Computed tomography and MRI have a sensitivity, specificity and accuracy of 75%, 70%, 69% and 83%, 84%, 83% respectively [22]. However, the presence or absence of an adrenal mass cannot accurately discriminate the two entities. Although specific issues have to be resolved, like standardization of the procedure and the use or not of ACTH, adrenal vein sampling (AVS) is the diagnostic gold standard and its use is increasing [23]. The method is highly accurate with 95% sensitivity and 100% specificity, but it is invasive and is best performed in few dedicated centers. Such centers also have a very low rate of complications (2.5%). In centers with low expertise a high number of unsuccessful procedures is reported (20%-25%), mostly because of difficulties in cannulating the right adrenal vein [24]. In a recent meta-analysis of 952 patients submitted to both CT/MRI and AVS, discrepant results were produced in 37.8% of the cases. Should therapeutic decision was based on non-invasive imaging alone, 19.1% of patients amenable to surgical treatment would have continued on medical treatment and most importantly, 14.6% would have suffered inappropriate surgical intervention for IHA, while in 3.9% the wrong adrenal would have been removed [25]. In the aforementioned PAPY study [12], when AVS was used, APA was identified in 62.5% of the cases and IHA in 37.5%, whereas in the absence of confirmatory AVS respective rates were 28% and 72%. In that study almost 5% of the newly diagnosed hypertensive patients who were referred to specialized centers had surgically curable APA. However, even in centers performing AVS, this procedure is not offered to all patients with confirmed PA. In a recent survey from 20 such centers worldwide, the percentage of patients in whom AVS was performed was 77% (median value) but ranged widely between 19% and 100% [26].

Adrenal cortical scintigraphy in PA

Imaging of the adrenal cortex has been accomplished with the use of ^{131}I-6β-iodomethyl-19-norcholesterol (iodocholesterol, NCL-6-I, NP-59) and selenium-75-6β-iodomethyl-19-norcholesterol. The latter is not available since many years, while the former is recently also not available in many European countries. In USA there is no FDA approval for the use of either tracer. Mechanisms of iodochoresterol uptake are identical to those of unlabelled cholesterol. Cholesterol bound to low-density lipoproteins (LDL) in blood enters the adrenal cortex cells through LDL receptors which are regulated by ACTH. Once inside the cells iodocholesterol does not follow the cholesterol's metabolic pathway but is only esterified for storage. Before NP-59 administration, stable iodine (Lugol's solution, or super-saturated potassium iodide) should also be given to protect thyroid from unbound radioiodine [27]. The dose of NP-59 is usually 37MBq/1.73m^2, administered slowly intravenously and seldom produces side effects [28]. Under baseline conditions normal adrenal glands are detected a few days after NP-59 injection, when adrenal tracer concentration exceeds background activity. The adrenal uptake in normal subjects ranges from 0.075% to 0.26% (mean 0.16%) of the administered dose [27]. For the investigation of PA, NP-59 is given after dexamethasone suppression (Table 1) in order to enhance the functional difference between the zones of the adrenal cortex and also to reveal areas of autonomic function [29]. About 50% of adrenal uptake is dependent upon the trophic influence of ACTH, while 25% is modulated by the renin-angiotensine II axis. Approximately 40% of NP-59 uptake cannot be suppressed thereby allowing visualization of the normal adrenal glands on delayed im-

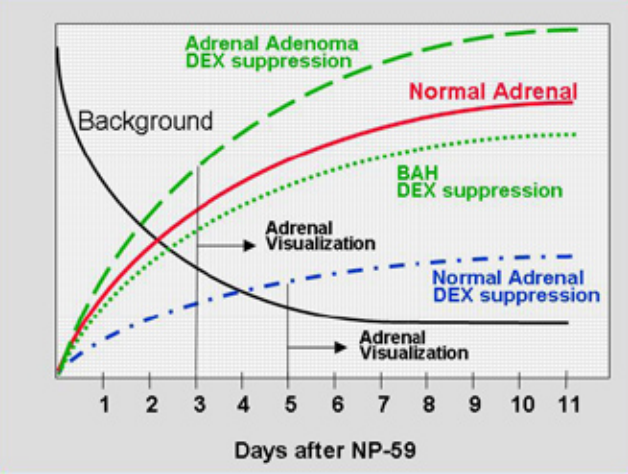

Figure 1. The pathophysiological basis of adrenal scintigraphy in PA. Normal adrenals are usually visualized a few days after NP-59 administration, at a time that the gradually increasing adrenal tracer uptake surpasses decreasing background activity. When uptake is partially suppressed by dexamethasone (DEX), normal glands are visualized usually on day 5 or later. Hyper-functioning adrenals are visualized earlier than day 5, even under dexamethason suppression.

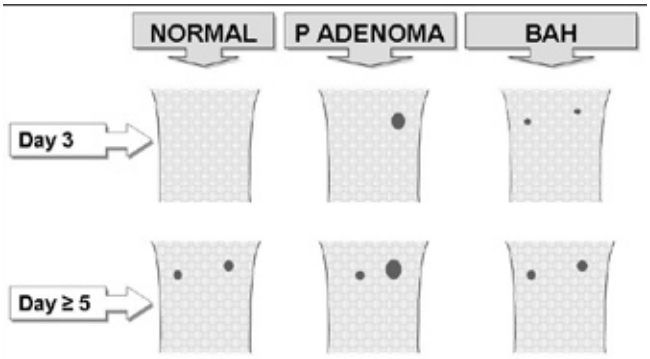

Figure 2. Dexamethasone suppression NP-59 scintigraphy in PA. Schematic representation of scintigraphic patterns.

Table 1. *Dexamethasone-supression NP-59 scintigraphy*

Sty	Study protocol
A.	A. Patient preparation
Su	Supression with dexamethasone (1mgx4 per day starting 7 days before NP-59 injection an for for 5 days thereafter)
Lu	Lugol's solution 2-3 drops twice daily, 48h before and for 7-10 days after NP-59 injection.
Dr	Drug discontinuation
Spi	Sprironolactone for 6 wks
Di	Diuretics for 2 wks
Bet	Beta blockers for 1 wk
AC	ACE inhibitors for 48h
Ca	Calcium channel blockers for 24h
Al	Alpha blockers and centrally acting anti-hypertensive drugs for 12h
B.	B. NP-59 injection at a dose of 37MBq/1.73m2
C.	C. Imaging
Da	Day 3. Planar (anterior, posterior and oblique views) and SPET (or SPET/CT)
Da	Day >5. Planar (anterior, posterior and oblique views) and SPET (or SPET/CT)

aging times. Normally, no focal finding is produced prior to the fifth day from tracer injection, but thereafter adrenal glands can be visualized due to "escape" from dexamethasone suppression (Fig. 1). Early (before day 5), unilateral adrenal visualization indicates APA or UHA, whereas bilateral detection means IHA [30]. Patterns of dexamethasone-suppression NP-59 scintigraphy are schematically presented in Figure 2. In the unusual case of GRA there may be bilateral non-visualization [31], while positive NP-59 findings are reported in some mineralocorticoid-secreting adrenal cortical carcinomas [32]. Classically, many anti-hypertensive drugs have to be discontinued before the examination, posing significant problems in blood pressure control during the procedure (Table 1) [29]. However, a recent study including 119 patients suggested that valid results can be produced without drug discontinuation [33]. Hypercholesterolemia can also influence scintigraphic results.

From an analysis of previous studies conducted between 1979 and 2003 which enrolled a total of 686 patients, the mean sensitivity of NP-59 scintigraphy was 86%, the specificity 78% and the accuracy 82% [22]. Only planar images were obtained in most of these studies. At present few centers include NP-59 scintigraphy in their diagnostic algorithms [22, 34], mainly where AVS is not available. Planar scintigraphy suffers from limited spatial resolution and reduced image contrast. Small (<1.5cm) adenomas, which are the most common, can hardly be recognized. Moreover, the interference of liver and intestinal activity poses many interpretation problems (Fig. 3). Some of the drawbacks of planar imaging are overcome by SPET, but due to the lack of anatomic landmarks image interpretation remains difficult. Recently, in small case series until now, encouraging results have been reported with the use of the new hybrid SPET/CT technology [35, 36]. Apart from image contrast enhancement attained by the implementation of attenuation correction, hybrid imaging permits correct localization of findings by incorporating anatomical and functional information. SPET/CT can identify small adenomas (0.8-1.5cm) [37, 38] even in patients with chronic renal disease where the biochemical proof of PA is difficult [39]. Our experience from the use of SPET/CT in our department is in line with the favorable literature reports. Figures 4 and 5 illustrate the advantages of SPET/CT in two cases of IHA (BAH). However, NP-59 SPET/CT has to prove its usefulness in larger prospective studies and in comparison with AVS, in order to regain its place in the diagnostic algorithms of PA. An accurate non-invasive method for identification of the cause of PA is still needed.

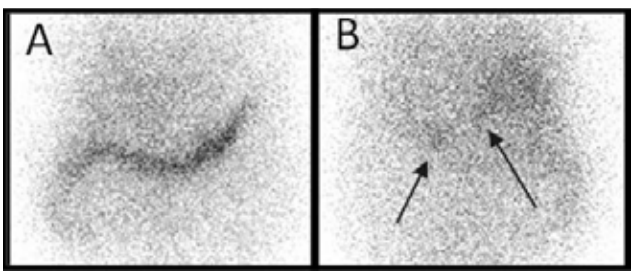

Figure 3. A: anterior and B: posterior NP-59 planar images 3 days after tracer administration under dexamethazone suppression. The arrows point at possible sites of the adrenal glands. Image contrast is poor and the visualization of the right adrenal is obscured by overlapping liver and intestinal activity. *(Images from the department of Nuclear Medicine University Hospital Rion-Greece)*

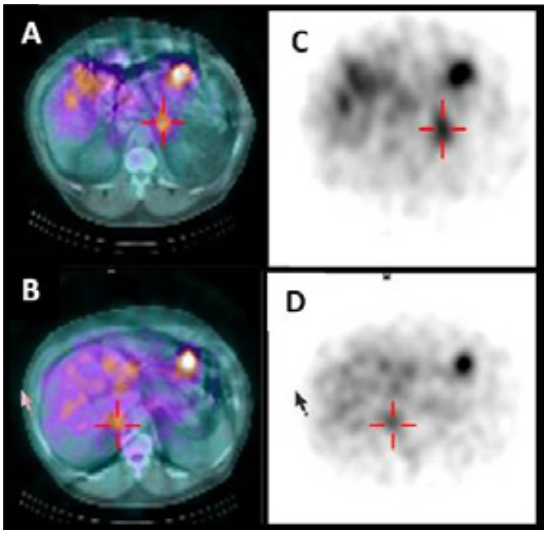

Figure 4. The SPET/CT study of the same patient (Fig. 4) at day 3. A and B are the fused SPET and CT images of the left and right adrenal and C and D the respective SPET images. There is clear visualization of both adrenals confirming IHA (BAH). *(Images from the department of Nuclear Medicine University Hospital Rion-Greece)*

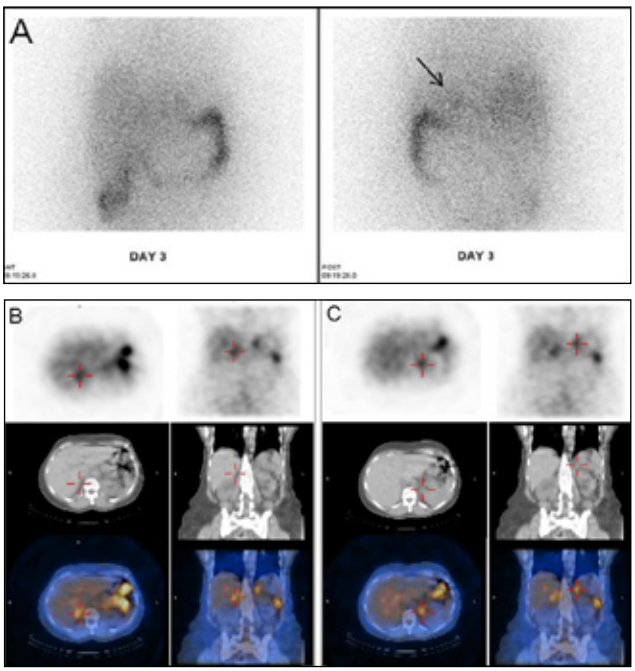

Figure 5. A case of IHA imaged with NP-59. A: Planar images demonstrate early visualization of the left adrenal (arrow) thereby falsely suggesting APA. Identification of the right adrenal is obscured by superimposition of liver activity which is high on day 3. B: and C: SPET/CT performed on the same day permits early detection of both adrenal cortices, which leads to the correct diagnosis of IHA (BAH). *(Images from the department of Nuclear Medicine University Hospital Rion-Greece)*

Lately, metomidate labeled with ^{11}C (^{11}C-MTO) has been used for adrenal cortex imaging [40, 41] with PET scanners. Metomidate is an inhibitor of 11β-hydroxylase and of the synthetase of aldosterone. It is involved in the production of cortisol and aldosterone and so its uptake is confined to adrenal cortex. Also ^{123}I-iodometomidate (^{123}I-IMTO) suitable for SPET and SPET/CT systems is under investigation [42]. Very recently a study has been published on the use of ^{11}C-MTO PET/CT in 39 patients with PA, compared with the AVS results. Patients were imaged with and without dexamethasone suppression. Dexamethasone increased tumor to nor-

mal adrenal SUV maximum ratio by 25.6±5.0% (P<0.01). Results of that study are encouraging, showing 87% specificity and 76% sensitivity for indentifying the site of aldosterone hypersecretion [43].

In conclusion, PA is much more common than previously considered. Its diagnosis is of primary clinical importance for choosing the correct treatment. The gold standard for discrimination between unilateral and bilateral disease is AVS. Imaging methods are less accurate in tailoring therapeutic decisions. Till now, only a few centers have used ^{131}I NP-59 for the investigation of PA. The interest in adrenal cortical scintigraphy has been renewed by the use of SPET/CT, but its value has to be proved in large patients' series with reference to AVS.

The authors declare that they have no conflicts of interest.

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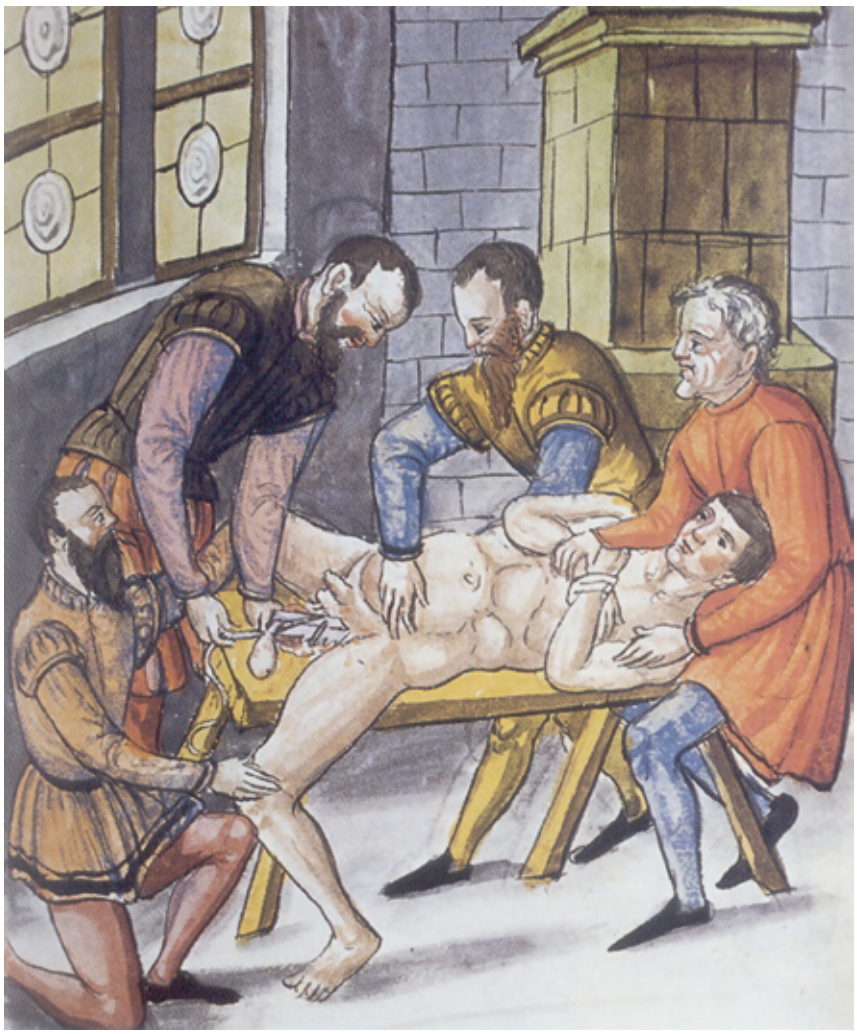

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