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Adrenocortical SPECT Using Iodine-131 NP-59

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Adrenal scintigraphy with ^{131}I-labeled 6-beta-iodomethyl-19-norcholesterol (NP-59) is a technically demanding and complex procedure. However, it can provide crucial and unique information about the functional status of the adrenal glands and guide the appropriate therapeutic management of patients with biochemically proven disease. Since the introduction of this new investigational drug, scintigraphic imaging has been performed using conventional planar techniques. We present an interesting case of primary aldosteronism in which planar scintigraphy and SPECT were combined in an attempt to increase the sensitivity of the study. SPECT revealed scintigraphic evidence of bilateral adrenocortical hyperplasia. Interestingly, the CT scan of this patient showed only an equivocal abnormality in the left adrenal gland, suggestive of an adenoma.

Key Words: primary aldosteronism; b-beta-iodomethyl-19-norcholesterol; SPECT

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Primary hyperaldosteronism is a rare cause of low-renin hypertension, representing only about 1% of hypertensive patients (*1*). It can result from a tumor (a benign unilateral adrenocortical adenoma in 75% of patients) or bilateral adrenal hyperplasia (*2*). Adrenal carcinoma is very rare (*3,4*). The distinction between different causes of primary aldosteronism is of utmost importance, because treatment options differ. Adrenal adenomas are best treated surgically, whereas adrenal hyperplasia is best treated by medical management (*5*). Radiopharmaceutical scintigraphy with dexamethasone-suppression technique has long been used to help differentiate between these causes using NP-59. The purpose of this pharmacological maneuver is to suppress the tracer into the large pool of cells that depend on adrenocorticotropic hormone (ACTH) for function (zona fasciculata and zona reticularis) and in turn enable the detection of tracer in tumors or hyperplastic tissues that are small but ACTH independent in function located in the outer zone (zona glomerulosa) (*6*). We present a case in which planar scintigraphy and SPECT were combined to image a patient with biochemical evidence of hyperaldosteronism. The sensitivity of the test to detect disease was clearly increased by combining these techniques, and we have demonstrated that planar imaging alone may miss the correct diagnosis.

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CASE REPORT

A 59-yr-old man was referred to our endocrine service for evaluation and management of hypertension and hypokalemia. Hypertension had been present for 9 yr. Serum potassium level was 2.5 mmol/liter (normal 3.6–5.0 mmol/liter), accompanied by a serum aldosterone of 26.3 ng/dl (normal 7–30 ng/dl) and a urinary potassium of 111 mEq/liter 124 hr. (normal 43–217 mEq/liter/24 hr). A collection for urinary-free cortisol had normal results. There was no family history of hyperaldosteronism. Potassium supplements helped relieve malaise. He admitted having mild upper-extremity paresthesias but denied muscle weakness, cramping or polyuria. An abdominal ultrasound study had shown a 10.5-cm cyst in the left kidney and two small cortical cysts in the right kidney, with normal bilateral renal artery flow (not shown).

Physical examination revealed generalized obesity without stigmata of Cushing's syndrome and a self-reported weight of 704 kg (320 lb). Supine blood pressure was 164/81 mm Hg with a pulse rate of 76 bpm.

While taking 50 mg hydrochlorothiazide, 75 mg triamterene, 40 mEq potassium chloride, 50 mg atenolol and 2 mg daily terazosin, a profile consistent with primary hyperaldosteronism was noted. The aldosterone-to-plasma renin activity (PRA) ratio was 120 with a low PRA of 0.10 ng/ml/hr (low-renin hypertension <0.65 ng/ml/hr). To eliminate medication effects, a 2-liter intravenous saline infusion suppression test was performed after all antihypertensive drugs had been discontinued for 2 wk. Serum aldosterone was 25 ng/dl before and 12 ng/dl after the 4-hr infusion, demonstrating a failure to suppress below 5 ng/dl. Serum 18-hydroxycorticosterone was 75 ng/dl (normal 5–80 ng/dl). Plasma renin levels were again low at 0.15 and 0.10 ng/ml/hr.

A 24-hr urine aldosterone excretion collected for the period immediately after the saline loading was also elevated at 27.4 μg/dl (normal 2.30–21 μg/dl). Suppression to <5 μg/dl is expected with salt loading or mineralocorticoid suppression. Serum aldosterone and plasma renin were 34 ng/dl and 0.10 ng/ml/hr, respectively, while on adrenal-suppressive doses of dexamethasone. CT scan demonstrated a normal right adrenal gland and a lobulated left adrenal gland, 2 cm in thickest transverse dimension with areas of hypointensity consistent with an adrenal adenoma. The patient was then referred for adrenocortical scintigraphy.

METHODS AND PROCEDURES

The patient was premedicated with 4 mg of dexamethasone orally in divided doses beginning 1 wk before and continuing throughout the imaging period, lasting 4 days postinjection. He was given 5 drops of Lugol's solution in a glass of water daily to block thyroidal uptake of free ^{131}I on the day of dosing and continued for

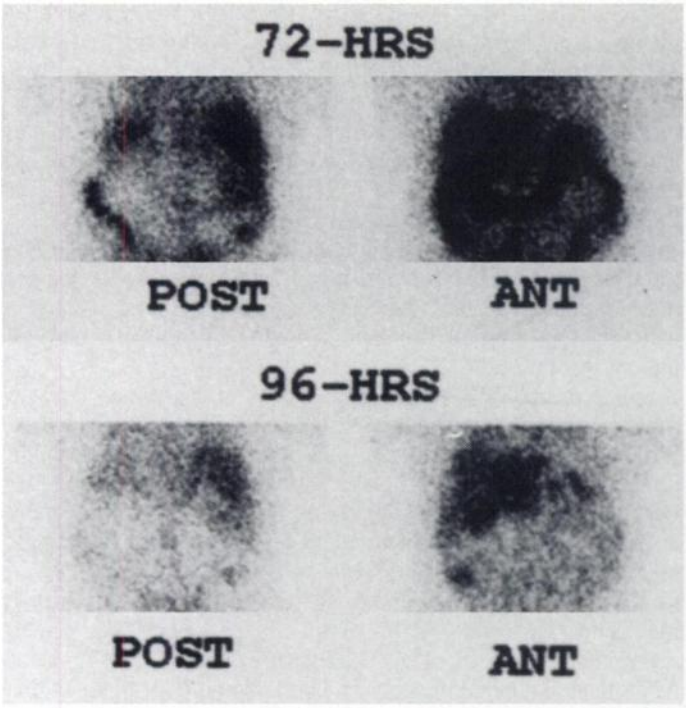

FIGURE 1. Planar posterior and anterior images of the abdomen 72 and 96 hr after tracer administration show normal biodistribution of the tracer with some bowel activity. No abnormal tracer localization was noted in the adrenal glands.

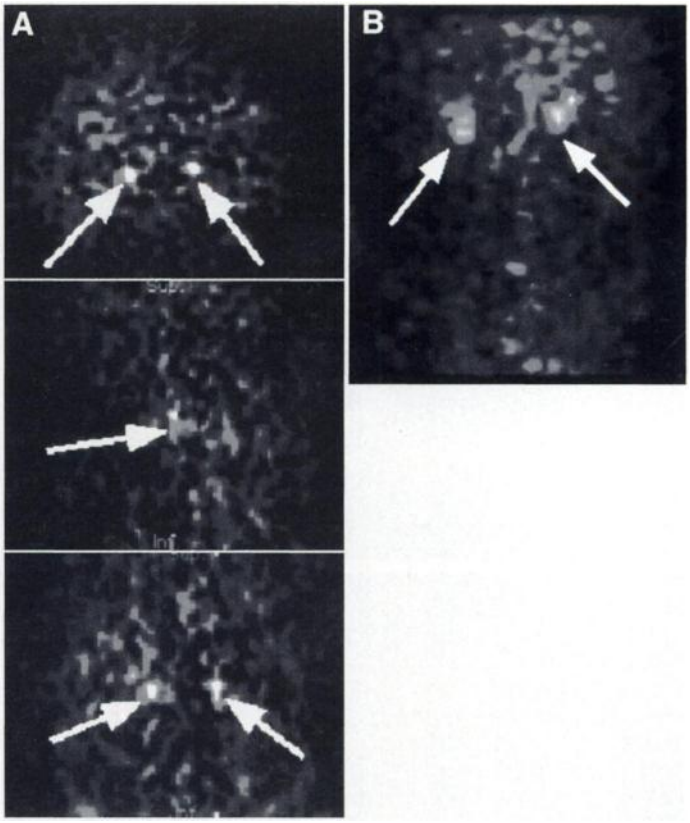

FIGURE 2. (A) SPECT image of the abdomen in transaxial, sagittal and coronal planes shows bilateral foci of increased tracer uptake in the regions of the adrenal glands (arrows). (B) Reprojected volume-rendered image reconstructed from the transaxial image confirms these abnormalities (arrows).

another week. Subsequently, 2 mCi NP-59 were administered by slow intravenous injection. The usual dose for optimal imaging is 1.0 mCi per 1.73 m^2 to a maximum of 2 mCi (*7*). In many series, a maximal dose of 1.0 mCi is used. A higher dose was given after considering the patient's habitus and the plan to obtain SPECT images.

Planar images of the posterior lumbar region were acquired 72 and 96 hr after injection using a BIAD gamma camera (TRIONIX, Twinsburg, OH) with a high-energy, parallel-hole collimator. Images were stored on a 128 × 128 matrix without zoom. SPECT images were also obtained on those two days using the following parameters: matrix size 128 × 128, no magnification and 50 sec/step × 45 steps. Raw data were processed by backprojection and prefiltered with a Hamming filter at 0.947 cycles/cm Nyquist and high cut frequency of 0.800 cycles/cm. Reprojected images were then generated from the transaxial slices. All of these images were reviewed on a DeltaManager System (Med Image, Ann Arbor, MI).

RESULTS

NP-59 adrenocortical scintigraphy with dexamethasone suppression revealed no tracer accumulation in the adrenal gland regions on the planar images (Fig. 1). SPECT (Fig. 2A) and reprojected images (Fig. 2B), however, showed bilateral uptake in the region of the adrenal glands (arrows) 72 and 96 hr after injection that was consistent with adrenal hyperplasia. Based on our study, the patient underwent medical management with an Aldactone antagonist (25 mg spironolactone twice a day) and a hypotensive agent (2 mg terazosin hydrochloride twice a day). His blood pressure and serum potassium have been under control since then. His latest serum potassium level was 4.2 mmol/liter (normal 3.6–5.0 mmol/liter).

Interestingly, CT scan (Fig. 3) showed an equivocal abnormality in the left adrenal gland suggestive of an adenoma and a normal right adrenal gland.

DISCUSSION

With the increasing availability of more sensitive and specific radioimmunoassays to determine PRA and plasma or urinary aldosterone, the clinician's ability to diagnose primary aldosteronism, particularly in early and subtle disease, has increased. The disease is rare and represents only about 1% of patients but is a cause of potentially curable secondary hypertension. About 75% of cases of primary aldosteronism are caused by solitary adenomas and the rest are due to adrenal hyperplasia. Aldosterone-secreting adrenocortical carcinoma is very rare. It is important to determine the pathological cause before any attempts at therapy because autonomous adenomas (aldosteronomas) are amenable to surgery, whereas hyperplasia is treated best with medical therapy, particularly aldosterone antagonists. Several invasive and noninvasive techniques have been validated with variable results for preoperative identification of unilateral disease. Currently, there is no procedure available, either invasive or noninvasive, that has a near-perfect specificity to differentiate these two forms of primary aldosteronism. Radiopharmaceutical scintigraphy has been used since the early 1970s for the functional evaluation of adrenocortical disorders (*8*). The first studies used ^{131}I-labeled 19-iodocholesterol; however, with the introduction of ^{131}I-labeled 6-beta-iodomethyl-19-norcholesterol (NP-59) at the University of Michigan-Ann Arbor, the diagnostic accuracy of scintigraphy has improved (*9*). This is due to the fact that NP-59 provides higher adrenal concentration and better imaging characteristics than the first radiopharmaceutical and has been in use since 1975. Despite the many advantages of adrenocortical scintigraphy, including physiologic information that is not provided by conventional imaging modalities, CT and, to some extent MRI, are now the usual initial imaging methods of choice in the evaluation and

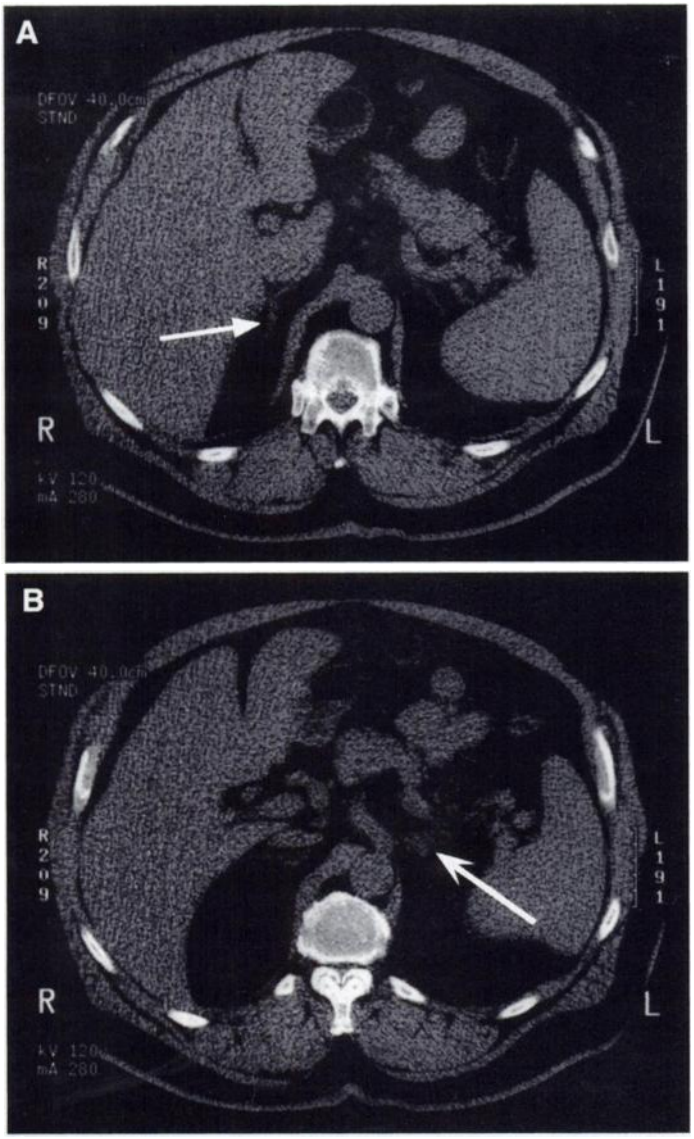

FIGURE 3. (A) Noncontrast transaxial CT slice shows normal right adrenal gland (arrow). (B) Adjacent transaxial slice shows lobulated left adrenal gland (arrow) measuring 2 × 3 cm with areas of low attenuation (7.1 H), consistent with an adenoma. In addition, the inferior pole of the left kidney contained a large cystic lesion (not shown).

anatomic detection of adrenal abnormalities. Although CT provides excellent anatomic resolution, its tissue specificity is suboptimal in most lesions except in uncomplicated cysts and myelolipomas, as reviewed by Francis et al. (*10*). MRI may have advantages over CT because of its ability to further characterize tissues but its value in the detection of small adrenal lesions may be limited by slice thickness capabilities (*11*) and lower spatial resolution than CT, particularly in the abdomen.

Weinberger et al. (*5*) compared four localizing techniques, namely adrenal venography, adrenocortical scintigraphy, modified adrenal venous sampling for steroid measurements and anomalous postural decrease in plasma aldosterone concentration in 51 patients with primary aldosteronism. The results from each technique were correlated with surgical findings. Correct localization was 47% with scintigraphy, 66% with adrenal venography and 91% with modified adrenal venous sampling. The sensitivity of scintigraphy was poor compared with previously reported series probably because of smaller lesion size, the resolution of the imaging equipment and the fact that some patients underwent scintigraphy without dexamethasone suppression. Interestingly, one patient had bilateral solitary adenomas and the scan showed localization on the left side both before and after dexamethasone suppression. Furthermore, their surgical cure rate for patients with adenomas was 68%, whereas that for bilateral hyperplasia was much less at 18%, which is in keeping with previously reported data (*12–14*). Adenomas and hyperplastic changes may be so small that they may not distort the adrenal anatomy, making conventional imaging less sensitive. Furthermore, anatomic studies may not always indicate the bilateral nature of the hyperplastic pathological process wherein one adrenal gland may be enlarged, and this finding may be interpreted as a unilateral adenoma. This was the case with the patient in our study.

Gross et al. (*15*) studied 87 patients with primary aldosteronism using dexamethasone-suppression adrenal cortical scintigraphy with NP-59. Planar posterior and lateral abdominal images were obtained on Days 3–5 after tracer injection. CT was also performed in 33 patients. The diagnosis of adrenal cortical adenoma was confirmed by surgery in 49 of 50 patients, and bilateral adrenal hyperplasia was confirmed by adrenal vein sampling in 33 patients and by surgery in 4. NP-59 correctly identified the lesions in 82 of the 87 patients. CT correctly detected adenomas in 14 of 23 patients, whereas 2 of 10 patients with bilateral adrenal hyperplasia had bilaterally enlarged adrenal glands, but 8 had normal anatomic findings. The modification of adrenocortical scintigraphy with the addition of dexamethasone has resulted in increased sensitivity and accuracy to 90%. The overall sensitivity and specificity of scintigraphy from this study was 96% and 94%, respectively (*15*).

The introduction of multidetector scintillation cameras with SPECT capability has improved image resolution of smaller lesions, facilitated shorter imaging time and, hence, increased the sensitivity of the studies without sacrificing specificity.

In our study, we diagnosed bilateral adrenal hyperplasia using SPECT with NP-59 and dexamethasone suppression. We have demonstrated that using the upper dose range for NP-59 (2 mCi) provides enough count statistics to perform tomography. Although a review of the literature suggests that tomographic imaging can be performed (*16,17*), we believe this is the first reported use of SPECT for adrenocortical scintigraphy in the diagnosis of hyperaldosteronism caused by bilateral adrenal hyperplasia.

NP-59 SPECT provided evidence that our patient had primary aldosteronism caused by bilateral hyperplasia. Although there was no proof of this diagnosis, the 18-hydroxycorticosterone levels and the response to therapy were in line with a diagnosis of primary aldoseteronism caused by bilateral hyperplasia.

CONCLUSION

We believe that SPECT should be performed by Day 4 after tracer administration if planar imaging fails to provide satisfactory data. This is best accomplished using the higher dose protocol. Although SPECT has not been used clinically in the past with NP-59 because of its radiopharmaceutical limitations, it may be a crucial test in patients who have definite biochemical evidence of primary hyperaldosteronism, particularly those patients with equivocal CT, MRI or planar scintigraphy findings.

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Increased Technetium-99m-GSA Uptake per Hepatocyte in Rats with Administration of Dimethylnitrosamine or Hepatocyte Growth Factor

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Technetium-99m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin (GSA) is a new scintigraphic agent that binds specifically to asialoglycoprotein receptors on hepatocytes, and can be used to evaluate hepatic function. Asialoglycoprotein receptor is a hepatocellular membrane receptor responsible for the endocytosis of asialoglycoproteins, and the function of this receptor is affected in various disease states. The aim of this study was to investigate GSA uptake per hepatocyte in the convalescent stage from hepatic damage. **Methods:** We used rats with dimethylnitrosamine (DMN)-induced hepatic injury and rats with recombinant human hepatocyte growth factor (rhHGF) stimulation. Plasma clearance of GSA and the number of hepatocytes in whole liver were calculated. **Results:** In the DMN-treated rats, the total number of hepatocytes and GSA plasma clearance were reduced significantly at 3 wk after the final administration of DMN. However, calculated GSA uptake per individual hepatocyte was significantly greater by 53.2% than in the normal controls. The area of hepatic nucleus was also significantly greater than in the normal controls. In the rhHGF-treated rats, an increase in the total number of hepatocytes was not demonstrated on the final day of rhHGF administration (Day 4). However, calculated GSA uptake per hepatocyte was significantly greater (59%) than in the controls. **Conclusion:** Augmented GSA uptake per hepatocyte during the convalescent stage after hepatic injury suggests a cellular compensation to the decreased number of hepatocyte. This mechanism may be caused by the secretion of some hepatotropic factors such as HGF.

Key Words: technetium-99m-galactosyl-human serum albumin; asialoglycoprotein receptors; hepatocyte growth factor; dimethylnitrosamine

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Technetium-99m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin (GSA) (Nihon Medi-Physics Chemical, Nishinomiya, Japan) is a new scintigraphy agent that binds specifically to asialoglycoprotein receptors (ASGPR) (*1*) on hepatocytes, and can be used to evaluate hepatic function (*2*). Diethylenetriaminepentaacetic acid has been used to obtain stable labeling with ^{99m}Tc (*3,4*).

Asialoglycoprotein receptor is a hepatocellular membrane receptor responsible for the metabolism of serum glycoproteins. Asialoglycoprotein receptor recognizes and binds galactose-terminated glycoproteins by a second-order chemical reaction (*5,6*). After binding, the glycoproteins are transported to lysosomes, where the ligands are catabolized, and the receptor recycles to the plasma membrane (*5,6*).

It has been reported that receptor levels are reduced in galactosamine-treated rats (*7*) and patients with chronic liver disease (*8*). Similarly, decreased ligand clearance from plasma has been observed in streptozotocin-diabetic rats (*9*). These results suggested alterations in expression of the receptor, whereas the in vivo studies addressed the ASGPR activity per body or liver weight. In contrast, the issue of whether the decreased GSA uptake by the liver is associated with a reduction in the function of each cell or the total number of hepatocytes has not been examined in detail.

In vitro studies have examined asialoglycoprotein uptake activity per hepatocyte under various conditions. Although there is an abundance of evidence for decreased binding of asialoglycoprotein by isolated hepatocytes in a variety of experimental liver injuries (*10–12*), increased binding has been observed in diethylnitrosamine-treated rats (*13*).

Increased hepatocyte growth factor (HGF) secretion has been demonstrated during hepatic damage in rats (*14,15*). Human HGF, which strongly stimulates deoxyribonucleic acid (DNA) synthesis and proliferation of hepatocytes, was originally purified from the plasma of patients with hepatic failure (*16*). Its