Dexamethasone-Suppression Adrenal Scintigraphy in Hyperandrogenism: Concise Communication

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Hyperandrogenism (HA) is a common endocrinopathy in women. Although estimates vary, its incidence ranges from 33 to 75% of female populations studied (1,2). There is a marked age-related increased incidence of HA in women 60 years or older (1). The manifestations of the problem are varied, and range from increased facial or body hair growth and menstrual irregularities (simple hirsutism) to temporal balding, deepened voice, clitoromegaly, and defeminization (virilization) (2,3). Studies of hirsute women have been hampered as a result of the complicated biochemical and invasive approaches required for diagnostic confirmation of the source(s) of excessive androgen production.

To assess the contribution of adrenal-derived androgens in women with hirsutism, adrenal scintigrams under dexamethasone suppression (DS) were performed on 35 women with increasing facial or body hair and irregular or absent menses. Based upon the DS regimen chosen (8 mg/d for 2 days or 4 mg/d for 7 days before the injection of 6\(\beta\)-[\(^{131}\)I]iodomethylnorcholesterol), three imaging patterns were identified. The first was the absence of uptake before 3 days (8-mg DS) or before 5 days (4-mg DS) after injection. This imaging pattern was seen in 17 of the 35 patients studied and was considered normal. The second pattern was bilateral uptake earlier than 3 days (8-mg DS regimen) or 5 days (4-mg DS) after injection. This was seen in 13 of the 35 patients and was interpreted as bilateral early visualization. Adrenal-vein catheterization performed on six patients with this pattern showed increased adrenal-vein testosterone. The third pattern, observed in five patients, was unilateral early visualization, which in four cases investigated to date was the result of an adrenocortical adenoma. This study confirms the adrenal cortex as a source of androgens in women with hirsutism and hyperandrogenism and demonstrates that DS adrenal scintigraphy can be utilized to identify those women in whom adrenal-derived androgens contribute to their hyperandrogenism.


Hyperandrogenism (HA) is a common endocrinopathy in women. Although estimates vary, its incidence ranges from 33 to 75% of female populations studied (1,2). There is a marked age-related increased incidence of HA in women 60 years or older (1). The manifestations of the problem are varied, and range from increased facial or body hair growth and menstrual irregularities (simple hirsutism) to temporal balding, deepened voice, clitoromegaly, and defeminization (virilization) (2,3). Studies of hirsute women have been hampered as a result of the complicated biochemical and invasive approaches required for diagnostic confirmation of the source(s) of excessive androgen production.

We have previously described the dexamethasone suppression (DS) adrenal scintigram in normal subjects and have demonstrated the efficacy of this noninvasive procedure to identify the source of excessive aldosterone production in primary aldosteronism (4–9). DS adrenal scintigraphy has also been utilized to identify the source(s) of excessive androgen production in women with hirsutism and hyperandrogenism (10–12). The present report describes our experience with DS adrenal scintigraphy in the assessment of adrenal disturbances in 35 women with hirsutism and hyperandrogenism.

METHODS

Thirty-five women referred for evaluation of hirsutism and hyperandrogenism were studied with 6\(\beta\)-[\(^{131}\)I]iodomethylnorcholesterol (NP-59)* DS adrenal scintig-
raphy. In this study, hirsutism was defined as increased facial or body hair and irregular or absent menses. All patients were investigated after written, informed consent was obtained.

Dexamethasone suppression was performed using either 8 mg of dexamethasone, administered daily in divided doses for 2 days (8-mg DS), or 4 mg administered daily in divided doses for 7 days (4-mg DS), before the injection of 1–2 mCi of NP-59, and continued throughout the imaging sequence. To suppress thyroidal uptake of free I-131, all patients received Lugol's iodine solution, three drops twice daily, beginning 48 hr before injection of NP-59 and continued throughout the imaging sequence. Posterior adrenal images were obtained at 48, 72, 96, and 120 hr after NP-59 administration, using a standard gamma camera equipped with a high-energy, parallel-hole collimator interfaced to a minicomputer. In selected cases, images were also obtained over the lower pelvis in an attempt to image ovarian tissue. For uptake calculations, left lateral images were obtained at 96 and 120 hr to estimate adrenal depth. Both analog and computer-enhanced digital images were recorded on Polaroid film.

The normal patterns of imaging using the 8-mg DS regimen would be bilateral adrenal activity seen later than 3 days after the injection, or bilateral adrenal visualization later than 5 days after injection under the 4-mg DS regimen (9). As a result, scans were interpreted as abnormal if adrenal visualization occurred before 3 days (8-mg DS) or 5 days (4-mg DS) after the injection of NP-59, or if significant lateralization of activity was seen on two successive days (9). Percent adrenal uptakes were calculated on the first day of discernible uptake, using a modification of the method of Koral and Sarkar (13).

Plasma testosterone, urinary 17-ketosteroids (17-KS) and 17-hydroxycorticosteroids (17-OHCS) were obtained on all patients pre-DS. Post-DS, plasma testosterone was obtained on 24 of the 35 patients and 17-KS on 21 of the 35 patients. Urinary 17-OHCS were obtained post-DS on all patients to assess the effectiveness of DS and to monitor patient compliance.

RESULTS

Clinical presentation and relation to patterns of imaging in hyperandrogenism. Three imaging patterns were identified under dexamethasone suppression. Seventeen of 35 patients had normal imaging patterns, showing no discernible adrenal activity for 3 days (8-mg DS) or 5 days (4-mg DS) following the administration of the tracer (Fig. 1). Thirteen of the 35 patients had bilateral early visualization (BEV), which occurred within 3 days (8-mg DS) or 5 days (4-mg DS) after the injection of NP-59, or if significant lateralization of activity was seen on two successive days (9). Percent adrenal uptakes were calculated on the first day of discernible uptake, using a modification of the method of Koral and Sarkar (13).

A definite separation of patients based upon the clinical manifestations of hyperandrogenism could not be made between the groups exhibiting the normal pattern and the bilateral pattern of imaging. The group of patients with the normal scan pattern presented with the excessive facial, extremity, and truncal hair. The menstrual histories of these patients were characterized by irregular menses (11 of 17). In some, sparse menses were noted with cessation of menstrual activity for variable intervals (6 of 17). The group of patients that comprised...
the BEV pattern presented with the same general complaints concerning body hair growth as the patients in the normal group. These patients also had severe menstrual dysfunction, with the majority experiencing amenorrhea. Moderate to severe virilization characterized by frontal balding, deepened voice, and amenorrhea was noted in the group of patients with the unilateral visualization pattern.

Results of dexamethasone suppression upon urinary 17-hydroxycorticosteroids, 17-ketosteroids, and plasma testosterone. Mean basal urinary 17-hydroxycorticosteroids (17-OHCS, normal range 5–10 mg/24 hr) were

\[
\begin{array}{cccc}
\text{Scan} & \text{Plasma testosterone}^* & \text{Urinary 17-ketosteroids}^* \\
\text{interpretation} & \text{(normal: 0.45 ± 0.21 ng/ml)} & \text{(normal: 4–14 mg/d)} \\
\text{Normal (N)} & 17/35 & 1.24 ± 0.22^\dagger & 0.81 ± 0.21 & 11.74 ± 1.58^\dagger & 6.7 ± 2.9 \\
\text{Bilateral early visualization (BEV)} & 13/35^\ddagger & 1.73 ± 0.22^\dagger & 0.90 ± 0.12 & 20.5 ± 3.5^\ddagger & 8.2 ± 1.2 \\
\text{Unilateral early visualization (UEV)} & 5/35^\ddagger & 2.42 ± 1.06^\dagger & 2.03 ± 0.99 & 19.28 ± 8.0^\ddagger & 13.1 ± 5.0 \\
\end{array}
\]

\* Mean ± s.e.m.
\^ Pre-DS vs DS. p < 0.05 by paired-t analysis.
\ddagger Six to date confirmed by adrenal-vein sampling: one had normal ovaries at laparotomy.
\ddagger Four confirmed at adrenalectomy: one by adrenal-vein vein sampling.
4.9 ± 0.86, 5.4 ± 0.94, and 5.0 ± 0.56 mg/24 hr in the normal, BEV, and UEV groups, respectively. Under dexamethasone suppression (normal ≥ 50% fall from basal), 17-OHCS fell to 1.2 ± 0.40, 1.0 ± 0.52, and 1.3 ± 0.34 mg/24 hr (p < 0.05) in the normal, BEV, and UEV groups, respectively.

As shown in Table 1, mean basal testosterone in both the UEV and BEV groups appeared higher than that observed in the normal group, but this elevation was not significant. In the two groups with early visualization, 17-KS were elevated and significantly higher than in the normal group. Dexamethasone suppression resulted in a significant fall of 17-KS in all groups (Fig. 4A). With the exception of one patient with an adrenal adenoma, testosterone fell significantly (p < 0.01) in all groups on DS (Fig. 4B). One patient with a normal scan (not included in Table 1) had basal serum testosterone of 4.5, 3.8, and 5.9 ng/ml, and urinary 17-KS of 13.6 and 14.0 mg/24 hr. On DS, plasma testosterone fell to 2.5 ng/ml and 17-KS to 4 mg/24 hr. Bilateral ovarian stromal hyperplasia was found at laparotomy, and after oophorectomy plasma testosterone fell to 0.22 ng/ml. No definite ovarian uptake of tracer could be observed on repeated imaging of the lower pelvis. Persistent, late bowel activity noted on all scans obscured the regions of expected ovarian activity.

Results of adrenal venous sampling—correlation with scan findings. To date, bilateral adrenal-vein sampling (AVS) has been performed in six of the 12 patients with the BEV pattern. In all six, adrenal-vein testosterone levels were greater than simultaneously obtained peripheral testosterone levels (Table 2). In one additional case, a laparotomy was performed with the presumptive diagnosis of polycystic disease of the ovary. At operation the patient had normal ovaries bilaterally. Ovarian-vein catheterization was not performed in any of these cases.

### TABLE 2. ADRENAL-VEIN CATHETERIZATION DATA FOR PATIENTS WITH EARLY BILATERAL IMAGING PATTERNS (BEV)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Adrenal vein testosterone (ng/ml)</th>
<th>Peripheral testosterone (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>(normal) 0.45 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13.2</td>
<td>1.2*</td>
</tr>
<tr>
<td>2</td>
<td>2.8</td>
<td>4.7</td>
</tr>
<tr>
<td>3</td>
<td>21.5</td>
<td>22.0</td>
</tr>
<tr>
<td>4</td>
<td>16.5</td>
<td>7.0</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>6</td>
<td>8.4</td>
<td>15.3</td>
</tr>
</tbody>
</table>

* Right adrenal vein not successfully catheterized.

Four of the five patients with UEV have had AVS performed to date. In all four, venous blood obtained from the side to which uptake lateralized showed a higher concentration of testosterone than the contralateral vein. Subsequently, four of the five adrenal adenomas were resected; the remaining patient is awaiting laparotomy.

**DISCUSSION**

In the hirsute woman, peripheral-blood androgens originate from the ovaries, the adrenals, and from peripheral conversion of androstenedione to testosterone (1–3,14). Androgen secretion by the adrenal gland is under adrenocorticotropin (ACTH) control, whereas the secretion of ovarian androgens is under the influence of the pituitary gonadotropin, luteinizing hormone. Previous studies in women with hirsutism and hyperandrogenism indicate that adrenal and ovarian suppression and/or stimulation tests do not reliably discern the origin of excessive androgen production in these patients (2,3,14). Both adrenal and ovarian androgens are suppressed by dexamethasone, estrogens, and/or progesterone (2,15,16). In this study, only half of the hirsute women had abnormal adrenal scans, yet most of the patients showed significant dexamethasone suppression of their serum testosterone and urinary 17-ketosteroid levels. Other factors that may be responsible for some of the problems that have been encountered in studies utilizing differential adrenal/ovarian suppression or stimulation tests are: (a) the presence of pulsatile pituitary ACTH and gonadotropin release; (b) significant peripheral conversion of precursor hormones to testosterone; (c) greater spontaneous swings in peripheral androgen levels in hirsute patients than in normal women; and (d) significantly higher production of adrenal androgen-precursor hormones in patients with polycystic ovarian disease (2,3,15,17).

In view of these problems, the localization of disease in the hirsute woman has relied in recent years upon combined adrenal- and ovarian-vein hormonal measurements. Results of these studies indicate that a great proportion of patients have ovarian-derived androgens as the primary source of their hyperandrogenism (1–3,18). Also noted in these studies, however, is the presence of concomitant excessive adrenal- and ovarian-derived androgens in a significant number of women (18–20). Table 3 is a compilation of catheterization studies from the recent literature documenting the incidence of this "combined" disease. These data demonstrate the presence of concomitant adrenal and ovarian hyperandrogenism in 17 to 80% in the reviewed series. Our present investigation confirms that a significant fraction (18 of 35 or 52%) of women with hirsutism appear to have an adrenocortical component to their disease.
The clinical manifestations of hyperandrogenism observed in these patients did not provide sufficient information to distinguish all but the most severe forms of the disorder. The correlation of the severity of the biochemical abnormalities and the clinical findings was limited to those with the severest forms of hyperandrogenism. Although elevated in all groups, plasma testosterone appeared to be a poor indicator of adrenal hyperandrogenism. No significant differences in plasma testosterone were observed between the groups studied. Urinary 17-KS were elevated in both the BEV and UEV groups. This parameter, although not sufficient to separate the BEV from UEV, did allow differentiation from the normal scan group. It appears that urinary 17-KS excretion may be predictive of those patients demonstrating an early pattern of adrenal visualization. The BEV and UEV groups do segregate by basal 17-KS levels; under dexamethasone suppression, however, the differences in urinary 17-ketosteroids between groups became less apparent. A possible explanation for the early visualization pattern seen in the BEV group may be that there is a proportion of nonsuppressible uptake that is accentuated under dexamethasone suppression, and it is this portion of the total uptake that accounts for the early and abnormal adrenal visualization. An anatomic correlate may be in the zona reticularis portion of the adrenal cortex, but the present study cannot further localize this abnormality. The pattern of imaging observed in the UEV group would suggest autonomous androgen production from an adrenocortical adenoma. Dexamethasone suppression in this group would result in suppression of iodocholesterol uptake into the contralateral adrenal cortex and thus provide localization of the neoplastic process.

Because combined catheterization and sampling of adrenal and ovarian veins was not performed in all patients studied, and in particular in those women with normal dexamethasone-suppression imaging patterns, we cannot assess the efficacy of adrenal imaging in hyperandrogenism. In addition, this study does not attempt to describe the ovarian component of the dysfunction in women with hyperandrogenism, since neither ovarian-vein sampling nor estrogen/progesterone suppression tests were performed. The finding of both normal basal and DS urinary 17-KS levels in the group with normal imaging patterns supports the presence of normal adrenal androgen secretion in these patients. This would leave the ovaries, or peripheral androgen-precursor conversion, as the most likely alternative sources of androgen hypersecretion in the patients with the normal scan pattern. These studies support the view that in at least one half of hirsute women adrenocortical abnormalities can exist by themselves or together with ovarian androgen hypersecretion (21–24).

Recent publications have established that adrenal scintigraphy is useful in the documentation and localization of adrenal disease. Adrenal tumors producing androgens have been described, and the location of such tumors was facilitated by their uptake of iodocholesterol (10–12,26).

Although testicular and ovarian uptake of NP-59 has been reported in cases of gonadal hyperfunction (27–29), we were unable to image the ovaries in the patients in whom this was attempted. This failure may be explained by (a) the small size of the ovary, (b) a low ovarian uptake of radiocholesterol (one fourth that of the adrenal), and (c) the location of the ovary in areas where background bowel radioactivity is high, especially in studies under dexamethasone suppression (9,30).

The present study describes our recent experience with DS-NP-59 adrenal scintigraphy in a group of hirsute women. Over half (18 of 35) of the patients studied had abnormal patterns of imaging. To date, 11 patients (seven of 12 with BEV and four of five with UEV) have undergone confirmatory procedures, all of which support the scan findings. The results of this study confirm those of other investigations showing a high proportion of adrenal or combined adrenal-ovarian disease in patients with hirsutism and hyperandrogenism using adrenal scintigraphic techniques.

FOOTNOTE

* NP-59 was obtained from the Nuclear Pharmacy, Univ. of Michigan Medical Center, Ann Arbor, MI.

ACKNOWLEDGMENT

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REFERENCES

2. JAMES VHT, RIPPON AF, JACOBS JS: Plasma androgens

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**New Orleans, Louisiana**

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