

Paradoxical Response to Dexamethasone in the Diagnosis of Primary Pigmented Nodular Adrenocortical Disease

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Background: Primary pigmented nodular adrenocortical disease causes the Cushing syndrome in children and young adults and is most frequently associated with the Carney complex.

Objective: To evaluate diagnostic tests for primary pigmented nodular adrenocortical disease.

Design: Retrospective cohort study.

Setting: Tertiary care center.

Patients: 21 patients with primary pigmented nodular adrenocortical disease. The control groups consisted of 9 patients with macronodular adrenocortical disease and 15 patients with primary unilateral adrenocortical disease (single adenomas).

Measurements: Clinical characteristics, radiologic imaging, and a 6-day Liddle test with determination of urinary free cortisol and 17-hydroxycorticosteroid excretion.

Results: Adrenal imaging and other tests were of limited value for the diagnosis of primary pigmented nodular adrenocortical disease. The Liddle test, however, distinguished patients with this disorder from those with other primary adrenocortical lesions. An increase of 50% or more in urinary free cortisol levels on day 6 of the Liddle test identified 9 of 13 patients (69.2% [95% CI, 46.6% to 91.8%]) with primary pigmented nodular adrenocortical disease, excluded all patients with macronodular adrenocortical disease, and was present in only 3 of the 15 patients with single adrenocortical adenomas (20% [CI, 0% to 40.2%]). An increase in urinary free cortisol excretion of 100% or more on day 6 of the Liddle test identified only patients with primary pigmented nodular adrenocortical disease.

Conclusions: Patients with primary pigmented nodular adrenocortical disease responded to dexamethasone with a paradoxical increase in glucocorticoid excretion during the Liddle test. This feature distinguishes such patients from those who have the Cushing syndrome caused by other primary adrenal disorders and may lead to timely detection of the Carney complex (a potentially fatal disorder) in asymptomatic patients.

Primary pigmented nodular adrenocortical disease is a bilateral adrenal disorder that leads to adrenocorticotropin (ACTH)-independent cases of the Cushing syndrome. In most cases, this disease occurs as part of the Carney complex, an autosomal dominant, multiple neoplasia syndrome that consists of skin lentigines, myxomas, and other nonendocrine and endocrine tumors (1). Cardiac myxoma, a tumor that may cause stroke and death, is among the most frequent and is often the first manifestation of the Carney complex (1, 2). The diagnosis of primary pigmented nodular adrenocortical disease should be followed by screening for the Carney complex and, in particular, its potentially fatal cardiac component (1, 2).

Establishing the diagnosis of primary pigmented nodular adrenocortical disease can be difficult because the associated hypercortisolism usually develops slowly over several years and the clinical manifestations may be subtle (3, 4). Results of radiologic imaging can be normal or indistinguishable from those that indicate adrenal nodularity, which is frequently present in other primary forms of the Cushing syndrome and in normal elderly persons (5). In addition, plasma ACTH levels may not be fully suppressed, especially in mild or periodic cases of the Cushing syndrome (3, 4). Previous reports have mentioned a paradoxical increase in glucocorticoid level after administration of various doses of dexamethasone in patients with primary pigmented nodular adrenocortical disease (6–11), but this observation has not been systematically investigated.

The Liddle test (12), the administration of low-dose and high-dose dexamethasone, is used to differentiate between pituitary-dependent and non-pituitary-dependent forms of the Cushing syndrome (12, 13). Suppression of urinary free cortisol greater than 90% and suppression of 17-hydroxycorticosteroid greater than 64% during the Liddle test identified all patients with pituitary-dependent cases of the Cushing syndrome in a large study of 118 patients (13). This test, however, has not been evaluated for its ability to differentiate between primary adrenocortical causes of the Cushing syndrome.

We analyzed data from 21 patients with primary pigmented nodular adrenocortical disease who had been evaluated at the National Institutes of Health

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(NIH) over the past 30 years. Sixteen patients underwent the Liddle test in addition to other testing. We compared the usefulness of the Liddle test in diagnosing primary pigmented nodular adrenocortical disease and in differentiating this disease from other primary adrenocortical disorders. For this purpose, we investigated two control groups of patients with primary adrenocortical diseases that lead to ACTH-independent cases of the Cushing syndrome: patients with macronodular adrenocortical disease, a condition that is almost always bilateral (14–16), and patients with unilateral, single adrenocortical adenomas.

Methods

Patients

We reviewed records of patients with ACTH-independent cases of the Cushing syndrome who were seen at the NIH clinical center over the past 30 years. The Carney complex was diagnosed on the basis of published criteria (2). Primary pigmented nodular adrenocortical disease, macronodular adrenocortical disease, and single adrenocortical adenoma were confirmed by histologic analysis after adrenalectomy or at autopsy, according to published criteria (1, 14–17). Macronodular disease, in particular, was diagnosed in the presence of multiple, bilateral, nonpigmented adrenocortical adenomas and a substantial increase in the weight of the adrenal glands (14–16). For some patients, little information was obtained about levels of plasma ACTH and urinary free cortisol because radioimmunoassays, which are now used to determine such variables, were not available until the late 1970s. The two control groups consisted only of patients for whom all data were available. For each patient, we analyzed plasma ACTH levels at 8:00 a.m.—followed by ovine corticotropin-releasing hormone stimulation—and diurnal plasma cortisol variation, as described elsewhere (13, 18). A 6-day Liddle test was conducted for each patient, as described elsewhere (12, 13): After 2 days of baseline measurement of urinary steroid excretion, dexamethasone, 0.5 mg, was given orally every 6 hours for 2 days starting at 6:00 a.m.; the dosage of dexamethasone was then increased to 2 mg every 6 hours for the last 2 days of the test. For children, the lowest dose of dexamethasone was adjusted to 7.2 $\mu\text{g}/\text{kg}$ of body weight and the highest dose was adjusted to 28.5 $\mu\text{g}/\text{kg}$ (3). In all patients, the 24-hour urinary free cortisol level was expressed per square meter of body surface area ($\mu\text{g}/\text{m}^2$); 17-hydroxycorticosteroid excretion was expressed per grams of creatinine excreted in 24 hours (mg/g). We also performed com-

puted tomography of the adrenal glands, as described elsewhere (19).

Hormone Assays

Plasma ACTH and cortisol levels were measured as described elsewhere (13, 18). Urinary free cortisol excretion was measured by using direct radioimmunoassay (20, 21). The intra-assay coefficient of variation was 5%, and the interassay coefficient of variation was 10%. Urinary 17-hydroxycorticosteroid excretion was measured by using a modification of the colorimetric method described by Porter and Silber (20, 21). The intra-assay and interassay coefficients of variation were 6% and 11%, respectively.

Statistical Analysis

All data are expressed as the mean \pm SE. For all statistical comparisons, a *P* value less than 0.05 was considered significant. Data were analyzed by using Statistica software (StatSoft, Inc., Tulsa, Oklahoma). Friedman analysis of variance was initially used within each group to determine differences in urinary free cortisol and 17-hydroxycorticosteroid levels in response to dexamethasone administration during the Liddle test. The Wilcoxon matched-pair test was used to determine which time points significantly differed from baseline. The Mann-Whitney U test was used to assess differences among groups. The specificity and sensitivity of the Liddle test were determined, and receiver-operating characteristic (ROC) curves were constructed, as described elsewhere (13, 18), to assess the usefulness of each method for differential diagnosis.

Results

Twenty-one patients (8 males and 13 females) with primary pigmented nodular adrenocortical disease were seen at the NIH clinical center over the past 30 years. Most patients were young: Age at diagnosis was 27.7 ± 2.9 years. Four patients were children (2 boys and 2 girls; age at diagnosis, 10 ± 1.8 years), and 17 patients were adults (6 men and 11 women; age at diagnosis, 31.9 ± 2.6 years). No children were included in the two control groups.

For 20 of 21 patients (95%), primary pigmented nodular adrenocortical disease occurred as a component of the Carney complex. Three of these patients had periodic cases of the Cushing syndrome (14%), which were characterized by periods of clinical symptoms and hypercortisolemia followed by periods of normalization of the body habitus and eucortisolemia, as described elsewhere (3, 4). The length of these periods varied considerably, from every 2 to 3 months (2 patients) to 1 to 2 weeks (1

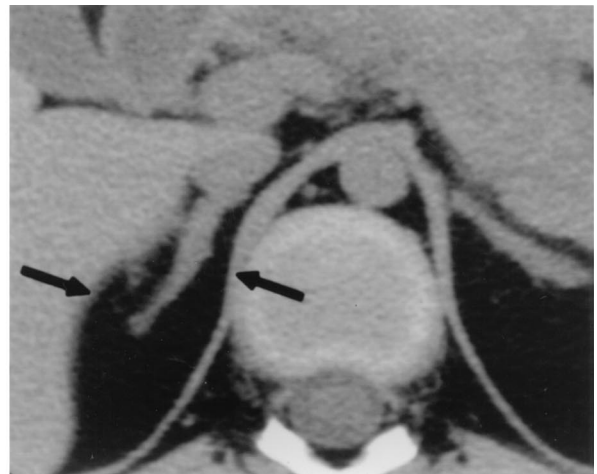
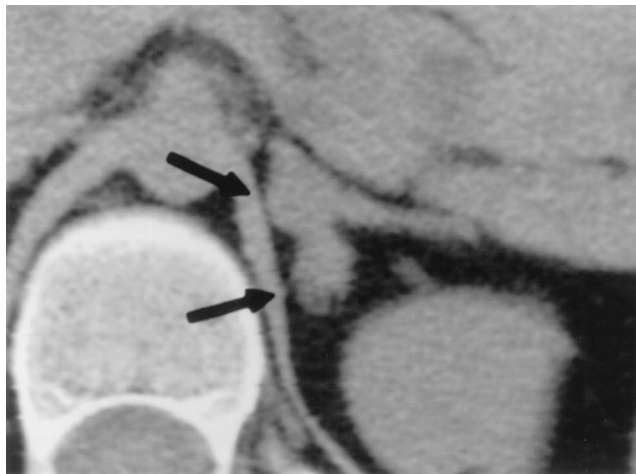


Figure 1. Macronodular appearance on computed tomography of the adrenal gland in a patient with primary pigmented adrenocortical disease (left) and the more typical "bead-on-a-string" appearance of an adrenal gland in a patient with primary pigmented nodular adrenocortical disease (right).

patient). Four patients with primary pigmented nodular adrenocortical disease (19%) had subclinical cases of the Cushing syndrome, which were characterized by a relative paucity of clinical findings of the syndrome (with the exception of osteoporosis) and eucortisolemia with abnormal diurnal cortisol variation, as described elsewhere (4).

Computed tomography revealed normal-sized adrenal glands in 19 patients with primary pigmented nodular adrenocortical disease (90%). Two patients had macronodules (nodules larger than 1 cm); one nodule had calcifications. An irregular contour of the adrenal glands, as described elsewhere (4, 5, 19), could be seen in 10 of the patients with primary pigmented nodular adrenocortical disease who had normal-sized adrenal glands (48%) (Figure 1). On computed tomography, all patients with macronodular adrenocortical disease had macronodules and all patients with single adenomas had a single mass.

Morning plasma ACTH levels were in the low end of the normal range but were still measurable in almost all of the patients in the three groups; however, no differences were seen in baseline ACTH values or responses of ACTH or cortisol to ACTH-releasing hormone stimulation ($P > 0.1$ for all comparisons, Mann-Whitney U test) (data not shown). All patients demonstrated loss or reversal of the normal pattern of diurnal cortisol variation, but no differences were seen among groups ($P > 0.1$ for all comparisons, Mann-Whitney U test) (data not shown).

Data were available for 16 patients with primary pigmented nodular adrenocortical disease who had 17-hydroxycorticosteroid or urinary free cortisol responses to the Liddle test. Thirteen of these 16 patients had both glucocorticoids measured; for 3 patients only 17-hydroxycorticosteroid measurements were available. In these 16 patients, urinary

excretion of both glucocorticoids increased gradually during the Liddle test (Figure 2). Friedman analysis of variance showed a P value less than 0.001 for 17-hydroxycorticosteroid and urinary free cortisol values in patients with primary pigmented nodular adrenocortical disease; the P value was greater than 0.2 for 17-hydroxycorticosteroid and urinary free cortisol values in patients with macronodular adrenocortical disease. For 17-hydroxycorticosteroid and urinary free cortisol values in patients with single adenomas, the P values were 0.05 and greater than 0.2, respectively.

In patients with primary pigmented nodular adrenocortical disease, the 24-hour excretion for both urinary steroids was significantly higher than baseline during the last day of the Liddle test. Specifically, for urinary free cortisol, the mean (\pm SE) baseline value was 306.6 ± 84.5 $\mu\text{g}/\text{d}$, whereas the value on day 6 was 620.2 ± 139.2 $\mu\text{g}/\text{d}$ (Wilcoxon matched-pair test, $P = 0.008$). For urinary 17-hydroxycorticosteroids, the baseline value was 11.6 ± 1.16 mg/mg of creatinine, whereas the value on day 6 was 23 ± 3.8 mg/mg of creatinine (Wilcoxon matched-pair test, $P = 0.017$). For four of these patients, who had atypical forms of the Cushing syndrome (periodic or asymptomatic), tests were done while they had normal baseline urinary free cortisol values.

Patients with macronodular adrenocortical disease ($n = 9$) as a group exhibited no statistically significant changes in glucocorticoid excretion during the Liddle test, and patients with single adenomas ($n = 15$) as a group exhibited changes only in 17-hydroxycorticosteroid levels. However, some patients from each group had a paradoxical, although moderate, response to dexamethasone. More specifically, glucocorticoid excretion increased 10% to 40% in four patients with macronodular adrenocor-

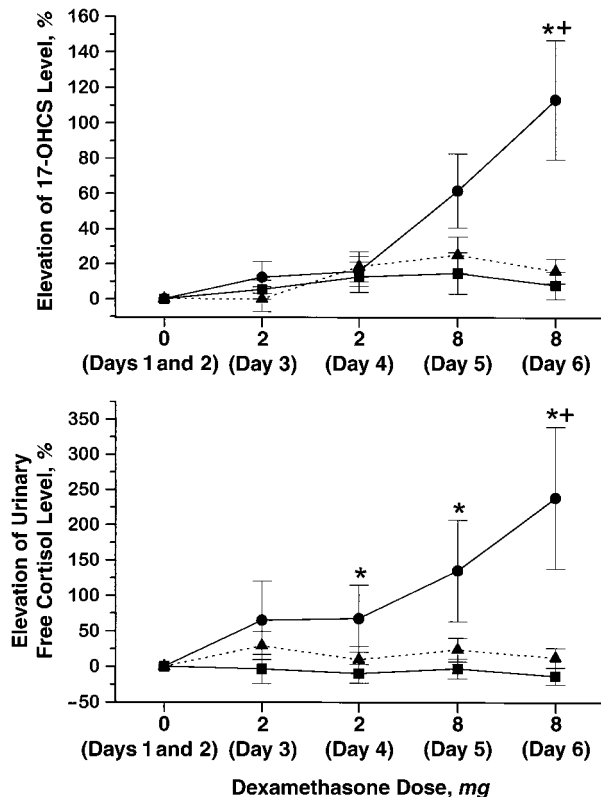


Figure 2. Mean percentage change in 24-hour excretion of 17-hydroxycorticosteroids (17-OHCS) (top) and urinary free cortisol (bottom) during the Liddle test. Circles represent patients with primary pigmented nodular adrenocortical disease, squares represent patients with macronodular adrenocortical disease, and triangles represent patients with single adenomas. The baseline value for both steroids is the mean of 2 days of 24-hour urine collection (days 1 and 2 of the Liddle test). Error bars represent the SE. *Statistical significance for patients with primary pigmented nodular adrenocortical disease compared with patients with macronodular adrenocortical disease (Mann-Whitney U test, $P < 0.001$ for all comparisons); +Statistical significance for patients with primary pigmented nodular adrenocortical disease compared with patients with a single adenoma (Mann-Whitney U test, $P < 0.01$ for urinary free cortisol level and 17-hydroxycorticosteroid level on day 6 of the Liddle test).

tical disease and approximately 50% in three patients with single adenomas (Figure 3).

We evaluated the degree of response to the Liddle test that would differentiate patients with primary pigmented nodular adrenocortical disease from patients with the other primary adrenocortical disorders. In patients with primary pigmented nodular adrenocortical disease, the percentage increase of urinary free cortisol levels on day 6 of the Liddle test (compared with baseline) was significantly higher than that seen in patients with macronodular adrenocortical disease or patients with single adenomas (Mann-Whitney U test, $P < 0.001$ and $P < 0.01$, respectively) (Figure 2). In addition, urinary free cortisol levels measured on day 6 had the greatest area under the ROC curve (0.86) (Figure 3). The percentage increase of 17-hydroxycorticosteroid levels on day 6 of the Liddle test was also significantly higher in patients with primary pigmented nodular adrenocortical disease than in pa-

tients with either of the other primary adrenocortical disorders (Figure 2) (Mann-Whitney U test, $P < 0.001$ for both groups). However, for patients with primary pigmented nodular adrenocortical disease, the area under the ROC curve for 17-hydroxycorticosteroid level was lower on day 6 of the Liddle test (0.75) (Figure 3). Baseline values for urinary free cortisol and 17-hydroxycorticosteroid levels yielded insignificant ROC curve areas (0.46 and 0.38, respectively) (Figure 3).

Urinary free cortisol levels on day 6 of the Liddle test provided the highest accuracy for the diagnosis of primary pigmented nodular adrenocortical disease. An increase of 50% or more in urinary free cortisol levels on day 6 identified 9 of 13 patients with primary pigmented nodular adrenocortical disease (69.2% [95% CI, 46.6% to 91.8%]), excluded all patients with macronodular adrenocortical disease, and occurred in only 3 of the 15 patients with a single adrenocortical adenoma (20% [CI, 0% to 40.2%]) (Figure 3). An increase in urinary free cortisol excretion of 100% or more on day 6 of the test identified only patients with primary pigmented nodular adrenocortical disease.

Discussion

Our study represents the largest series of patients reported to date with primary pigmented nodular adrenocortical disease. In our patients, the disease was almost always part of the Carney complex. Among the diagnostic tests used for the detection of this primary adrenocortical disorder, computed tomography of the adrenal glands has been suggested as the most helpful (5, 19). However, bilateral adrenal micronodules, which may suggest primary pigmented nodular adrenocortical disease (19), enlarge with age and become common in normal persons (5). Furthermore, the irregular contour (or "beads-on-a-string" appearance) of the glands on computed tomography is not observed universally, although it is characteristic of primary pigmented nodular adrenocortical disease (3-5) (Figure 1). Occasionally, glands in patients with primary pigmented nodular adrenocortical disease harbor macronodules (4) that are identical to those seen in patients with macronodular adrenocortical disease or single adenomas (5, 22). One such patient with the Carney complex, primary pigmented nodular adrenocortical disease, and large nodules was recently reported (23).

Biochemical investigation in patients with primary pigmented nodular adrenocortical disease may be equally unspecific. The Liddle test (12) is an essential test in the diagnostic algorithm leading to the detection of nonpituitary-dependent cases of the Cushing syndrome (12, 13, 24). With some notable

exceptions (9–11), it has been assumed that most patients with primary pigmented nodular adrenocortical disease would respond to dexamethasone during the Liddle test with lack of suppression, as would other patients with adrenocortical tumors (12, 13). However, it is remarkable that almost all our patients with primary pigmented nodular adrenocortical disease responded to dexamethasone with increased glucocorticoid excretion; this response was absent or only occasionally present in patients with other primary adrenocortical disorders.

Paradoxical responses to dexamethasone in the presence of an adrenocortical adenoma or carcinoma (25, 26) have been described in individual patient reports and were seen in two of Liddle's patients (12). However, in patients with single adenomas, such a response is rare and does not occur to the same degree as in patients with primary pigmented nodular adrenocortical disease. In contrast, a paradoxical increase in glucocorticoid levels in response to dexamethasone has been a feature of almost all reported patients with primary pigmented nodular adrenocortical disease and the Cushing syndrome (1, 3, 4, 6–11, 27–30). A review of the literature revealed only one patient with histologic confirmation of primary pigmented nodular adrenocortical disease and no increase in plasma cortisol levels, urinary 17-hydroxycorticosteroid levels, or urinary free cortisol levels in response to dexamethasone (27). This was one of the two patients described by Bohm and coworkers (27), in whom urine glucocorticoid levels decreased approximately 75% during the Liddle test. Of interest, the paradoxical increase of glucocorticoid levels in response to dexamethasone has also been reported in eucorticolemic patients with primary pigmented nodular adrenocortical disease (28).

Similar responses in patients with primary pigmented nodular adrenocortical disease have been documented in plasma cortisol level (29) after 0.5, 1, and 32 mg of oral dexamethasone (11, 28) or 5 mg of intravenous dexamethasone (30). Recently, two patients with primary pigmented nodular adrenocortical disease were reported to have paradoxical increases in serum and salivary cortisol levels after oral administration of 8 mg of dexamethasone (31). It is important to note that in our patients with primary pigmented nodular adrenocortical disease, the increase of glucocorticoid levels in response to dexamethasone was dose-dependent and that dose dependency was present only in patients with primary pigmented nodular adrenocortical disease; it was not present in the two control groups, which showed a similar, albeit smaller, increase (Figure 2).

Our data suggest that increased urinary 17-hydroxycorticosteroid and free cortisol levels during the Liddle test may be used to diagnose primary

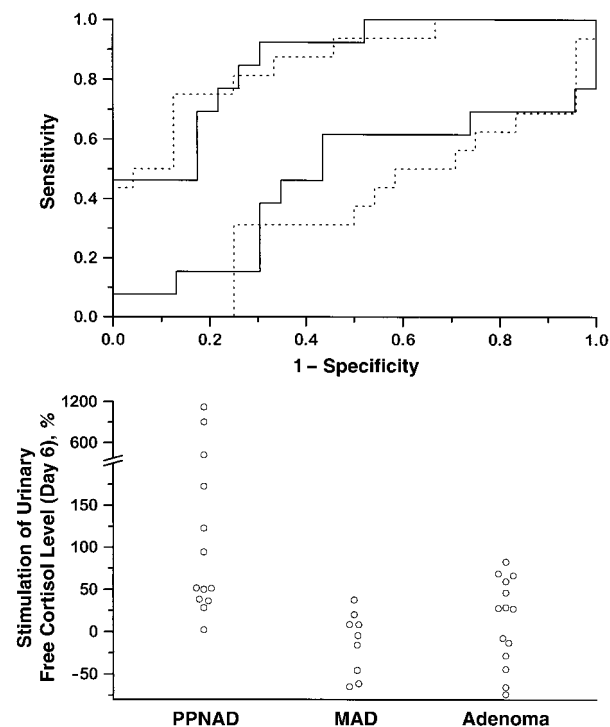


Figure 3. Receiver-operating characteristic curves and urinary free cortisol levels during the Liddle test. **Top.** Receiver-operating characteristic curves for urinary free cortisol level (solid lines) and 17-hydroxycorticosteroid level (dotted lines) in the diagnostic evaluation of primary pigmented nodular adrenocortical disease compared with other primary adrenal disorders during the Liddle test. The upper two curves represent urinary steroid values on day 6 of the Liddle test, and the lower two curves represent baseline urinary steroid values. **Bottom.** Urinary free cortisol levels. MAD = macronodular adrenocortical disease; PPNAD = primary pigmented nodular adrenocortical disease.

pigmented nodular adrenocortical disease. In our study, this marker was particularly useful for detection of this disease in four eucorticolemic patients who had other signs of the Carney complex but asymptomatic, atypical, or periodic forms of the Cushing syndrome. This test may be used to detect carriers of the Carney complex or isolated primary pigmented nodular adrenocortical disease. It may also be used to detect primary pigmented nodular adrenocortical disease in patients with nonpituitary-dependent cases of the Cushing syndrome and ambiguous findings on computed tomography or patients without a single, dominant adrenocortical adenoma.

The molecular cause of the dexamethasone-related increase of glucocorticoid levels in patients with primary pigmented nodular adrenocortical disease is unknown. Although this disease was originally suggested to be an autoimmune condition (32–34), adrenocortical antibodies have not been identified in most patients (2). The disorder is familial in half of the reported cases (1, 2) and is inherited in an autosomal dominant manner (2); it is genetically heterogeneous, and more than two genes and other genetic events may participate in its pathogenesis (35–37). In one in vitro experiment,

estradiol caused cortisol production by adrenal tissue cultured from one patient with primary pigmented nodular adrenocortical disease (38). A generalized, steroid-dependent interaction cannot be excluded; other investigators, however, have failed to show similar results (39).

Alternatively, aberrant expression of various substances may be responsible for this increase. The unexpected presence of synaptophysin immunoreactivity and other neuroendocrine features in patients with primary pigmented nodular adrenocortical disease (40) suggests that tissue in such patients differs substantially from that found in the adrenal cortex of normal patients. Similar paradoxical observations, primarily caused by aberrant expression of receptors for neuroendocrine molecules in the nodular tissue, have been described in patients with food-dependent cases of the Cushing syndrome and macronodular adrenocortical disease (41, 42). None of our patients with primary pigmented nodular adrenocortical disease had food-dependent cases of the Cushing syndrome, but one such patient has been reported (23).

We conclude that primary pigmented nodular adrenocortical disease occurs most frequently as part of the Carney complex and is associated with a paradoxical increase in urinary glucocorticoid excretion during the Liddle test. This test may be used for early diagnosis of primary pigmented nodular adrenocortical disease and the Carney complex.

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