Corticotropin-Independent Macronodular Adrenal Hyperplasia

A Clinicopathologic Correlation

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Objectives: To investigate the clinical presentation, laboratory findings, and pathologic characteristics of patients with corticotropin (ACTH)-independent macronodular adrenal hyperplasia.

Design: Retrospective review.

Setting: Academic medical center.

Patients: All patients with bilateral adrenocortical nodules associated with ACTH-independent hypercortisolism without clinicopathologic features of primary pigmented nodular adrenocortical disease with atrophic internodular adrenal cortex.

Main Outcome Measures: Compare and contrast our findings with those previously reported; assess response to adrenalectomy.

Results: Nine patients met the criteria for corticotropin-independent macronodular adrenal hyperplasia. All patients had biochemical evidence of Cushing syndrome, although repetitive testing was frequently required. As a result, the diagnosis was delayed from 1 to 20 years. In all patients, both the low- and high-dose dexamethasone suppression tests failed to suppress cortisol secretion. No patient had elevated ACTH levels, and following curative bilateral adrenalectomy, no patient subsequently developed Nelson syndrome, with follow-up ranging from 1 to 8.5 years. Unique histologic features were identified in all cases.

Conclusion: Amalgamating this series with other clinical reports plus basic research information, corticotropin-independent macronodular adrenal hyperplasia must be considered a separate and legitimate cause of Cushing syndrome.

Arch Surg. 1998;133:541-546

Since 1932 when Harvey Cushing first noted a constellation of signs and symptoms resulting from adrenal hyperplasia driven by a pituitary adenoma, our knowledge of Cushing syndrome has increased dramatically. Classification of Cushing syndrome according to etiology may be conveniently divided into corticotropin (ACTH)-dependent and ACTH-independent causes (Table 1). Nodular adrenocortical hyperplasia is uncommon, most typically seen in 20% to 40% of patients with Cushing disease, probably evolving as a later stage from diffuse hyperplasia that has been chronically stimulated by ACTH.1,2 Primary pigmented nodular adrenocortical disease (PPNAD) has been well established as a distinct, rare cause of Cushing syndrome, typically affecting younger patients whose adrenal glands are normal or slightly enlarged with numerous pigmented nodules and intervening atrophic nonnodular cortex.3,4

Recently, several case studies in the literature describing an ACTH-independent hypersecretion of cortisol associated with bilateral macronodular hyperplasia have been documented as a distinct, rare subtype of Cushing syndrome. Terms such as “ACTH-independent macronodular adrenal hyperplasia” (AIMAH), “ACTH-independent massive bilateral adrenal disease,” “massive macronodular hyperplasia,” “giant macronodular adrenal hyperplasia,” “macronodular adrenal hyperplasia,” and “macronodular adrenal dysplasia” have all been used to label this disorder. With its rarity and the multitude of suggested names and even with defining what constitutes the basic criteria, this disorder remains unclear. We expanded on the definition of AIMAH described by Aiba et al and Sasano et al and required the following characteristics be
PATIENTS, MATERIALS, AND METHODS

DIAGNOSIS

The diagnosis of Cushing syndrome was confirmed with measurements of morning and evening serum (normal morning range, 193-690 nmol/L; evening range, 55-386 nmol/L) and 24-hour urinary (normal range, 66-298 nmol/d) cortisol levels, and similar levels following the low-dose dexamethasone suppression test of 0.5 mg every 6 hours for 48 hours. A 24-hour urinary cortisol excretion of 55 nmol or higher following the dexamethasone suppression test establishes the diagnosis. The plasma ACTH level is measured (normal range, 0-13 pmol/L) to differentiate ACTH-dependent vs ACTH-independent Cushing syndrome. In addition, the results of the high-dose dexamethasone suppression test (dexamethasone, 2 mg, every 6 hours for 48 hours) fail to show suppression in urinary cortisol excretion in ACTH-independent hypercortisolism. This was the case in all 9 of our patients. It also helps to distinguish pituitary from ectopic ACTH hypersecretion as a decrease of 30% or greater in 24-hour urinary cortisol levels following high-dose dexamethasone is consistent with pituitary as the origin. A single 11 PM dose of 8 mg of dexamethasone with a 50% or greater suppression of 8 AM plasma cortisol was sometimes substituted for the standard high-dose dexamethasone suppression test. If equivocal levels of ACTH were obtained, inferior petrosal sinus sampling with ovine corticotropin releasing hormone stimulation was used, although this was only necessary in a single case. Computed tomography was critical and definitive in demonstrating the bilateral nodular adrenal glands in our patients with AIMAH.

FOLLOW-UP OF DEMOGRAPHIC, CLINICAL, AND OPERATIVE DETAILS

A review of patient files from 1977 through 1995 at Mayo Clinic in both Rochester and Scottsdale revealed 9 cases of AIMAH. The data extracted from the records included demographic characteristics, medical history and physical examination findings, laboratory and radiologic test results, operative procedures, hospital course, and postoperative follow-up.

PATHOLOGIC FINDINGS

A single experienced endocrine pathologist (R.V.L.) reviewed all adrenalectomy specimens with specific focus on adrenal gland weights and the size and color of nodules (none could be darkly pigmented [all were yellow cortical nodules]). Histologically, besides verifying that the nonnodular cortex was atrophic, the nodules were assessed for the presence of clear and compact cells with a lack of a definite capsule as well as the presence of cortical cell hyperplasia.

RESULTS

Nine patients fulfilled the criteria of AIMAH as we defined them; all had bilateral yellow nodules with atrophic nonnodular intervening cortex, and the ACTH levels were normal or suppressed (Table 2). Seven women and 2 men with a mean age of 56 years composed our series, and hypertension was noted in all but 1 patient. Subtle signs or symptoms consistent with Cushing syndrome were noted in these patients’ histories dating back as far as 20 years. Serum cortisol levels were elevated and/or demonstrated loss of diurnal rhythm. All patients failed to show suppression of cortisol excretion with both the low- and high-dose dexamethasone suppression tests.

Bilateral adrenal nodules were seen by computed tomographic scans in all patients, an example of which is seen in Figure 1.

OPERATION AND FOLLOW-UP

All patients underwent bilateral adrenalectomy, and all except patient 6 (who underwent bilateral laparoscopic adrenalectomy) required an open approach. Complications occurred in only 2 patients, one with a deep vein included in our series: (1) bilateral adrenocortical nodules that (2) are associated with ACTH-independent hypercortisolism but (3) are without the clinicopathologic features of PPNAD and with (4) histologically atrophic internodular cortex (consistent with cortisol suppression).

Approximately 40 cases of AIMAH have been reported in the literature. To investigate the clinical presentation, laboratory findings, and pathologic characteristics, we retrospectively reviewed the data from 9 patients treated at Mayo Clinic, Rochester, Minn, and Scottsdale, Ariz, who fit the above-cited criteria for AIMAH. In addition, we intended to compare and contrast our findings with those previously reported.

Table 1. Origin of Cushing Syndrome

<table>
<thead>
<tr>
<th>ACTH dependent</th>
<th>Pituitary glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin adenoma</td>
<td>Corticotropin multinodular hyperplasia</td>
</tr>
<tr>
<td>Corticotropin carcinoma</td>
<td>Ecopic</td>
</tr>
<tr>
<td>ACTH-secreting tumor</td>
<td>CRH-secreting tumor</td>
</tr>
<tr>
<td>ACTH independent</td>
<td>Unilateral adrenal gland</td>
</tr>
<tr>
<td>Adenoma</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Bilateral adrenal glands</td>
<td>PPNAD, primary pigmented nodular adrenocortical disease</td>
</tr>
<tr>
<td>Macronodular hyperplasia</td>
<td></td>
</tr>
</tbody>
</table>

*ACTH indicates corticotropin, CRH, corticotropin-releasing hormone, and PPNAD, primary pigmented nodular adrenocortical disease.
thrombosis and another with a pneumothorax. During follow-up that ranged from 1 to 8.5 years, Nelson syndrome had not developed in any patient.

**PATHOLOGIC FINDINGS**

As seen in Table 3, all patients showed what has been described as “unique morphologic features that are distinct from those seen in other types of nodular hyperplasia that cause Cushing syndrome.” Bilateral adrenal cortical nodules, ranging in size from 1 to 4.2 cm, were identified within adrenal glands weighing from 16.7 to 218 g combining both glands. Histologically, each gland displayed small clear cells with others also showing nests of compact cells with eosinophilic cytoplasm (Figure 2). The nodules were interpreted as showing variable degrees of hyperplasia, and the nonnodular cortex was comparable in the extent of cortical atrophy to that seen in the unaffected cortex of single cortisol-producing adenomas. Nuclear pleomorphism was uncommon and mitotic figures were rare.

**COMMENT**

Since the first described case of AIMAH by Kirschner et al., reports detailing from 1 to 6 patients have accumulated lending credence to its existence as a truly separate cause of Cushing syndrome. At variance from the general patient with Cushing syndrome are certain interesting observations such as a male predominance and discovery of the diagnosis a decade later than usual at age 52 years. Our male-female ratio is opposite to the generally reported experience, but no specific cause for a sex bias has been identified and may represent a random event. Moreover, an equal sex distribution is suggested by data that support, at least in some cases, a genetically transmitted pattern: a mother and daughter, 2 brothers, a brother and sister, and 2 brothers and a sister.
Considerable question surrounds the veracity of any proposed new disease or disorder, specifically if it resembles a preexisting and well-recognized condition. Smals et al\textsuperscript{16} and Hermus et al\textsuperscript{1} present convincing evidence that with continued, long-standing ACTH stimulation, hyperplastic adrenal cortex eventually becomes nodular and evolves into varying degrees of adrenal autonomy. In contrast to the patients in the present series, however, the internodular cortex in patients with long-standing ACTH stimulation remains hyperplastic and is therefore different from our as well as virtually all patients with AIMAH.

Through the work of several independent investigators, the data generated can be aggregated to form a cohesive hypothesis that describes the pathogenesis of AIMAH. The facts to support such a hypothesis derive from 4 separate but interrelated lines of evidence: clinical and biochemical data, unique histologic features, characteristic steroidogenic enzymes, and in vitro cell culture behavior. There is no question that the clinical picture of these patients is clearly one of ACTH-independent hypercortisolism. The fact that the serum ACTH level is suppressed, that high-dose dexamethasone administration always fails to produce cortisol suppression, and that there are virtually no cases of subsequent Nelson syndrome following bilateral adrenalectomy provide ample proof that the end point is ACTH independent. However, the process to reach that end point still remains the issue of debate. The suppressed, atrophic nonnodular cortex provides the link between the biochemical data and the revealing histologic features of AIMAH.

As a direct consequence of the autonomous cortisol secretion by the macronodules, the internodular cortex is atrophic. Even beyond this, however, the histologic characteristics and cellular ultrastructure have been carefully studied\textsuperscript{5} and appear unique. The adrenal glands are composed of an increased number of small clear cells in cordlike arrangements often accompanied by nesi-forming compact cells. The great majority of these cells show weak to negligible enzymatic activity and poorly developed smooth endoplasmic reticulum.

The purification and characterization of steroidogenic enzymes such as cytochrome P450 have led to the production of antibodies to these enzymes as well as to probes to the encoding messenger RNAs. Studies in patients with AIMAH have demonstrated that cytochrome P450c17 is not produced in the majority of clear cortical cells, and the compact cortical cells do not synthesize 3β-hydroxysteroid dehydrogenase—a pattern unique to AIMAH that has not been observed in other adrenocortical lesions associated with Cushing syndrome.\textsuperscript{6,8} This unique localization of steroidogenic enzymes in AIMAH is essential for steroid synthesis and autonomous cortisol secretion.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Adrenal Gland Weight, R/L, g</th>
<th>Maximum Nodule Size, cm</th>
<th>Histologic Findings, R/L</th>
<th>Internodular Cortex Atrophy</th>
<th>Degree of Nodular Hyperplasia</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3.1/13.6</td>
<td>1/3.1</td>
<td>C1, C/C1</td>
<td>Yes</td>
<td>1+/2+</td>
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<td>2</td>
<td>40/34</td>
<td>3.4/3.5</td>
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<td>Yes</td>
<td>2+/2+</td>
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<td>3</td>
<td>7.6/10.3</td>
<td>2.2/2</td>
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<td>Yes</td>
<td>2+/2+</td>
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<td>4</td>
<td>12/7.6</td>
<td>4/2.7</td>
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<td>Yes</td>
<td>3+/3+</td>
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<td>5</td>
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<td>6</td>
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<td>7</td>
<td>101/117</td>
<td>4/2.4</td>
<td>C</td>
<td>Yes</td>
<td>3+/3+</td>
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<tr>
<td>8</td>
<td>22/25</td>
<td>2/2.5</td>
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<td>Yes</td>
<td>3+/3+</td>
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<td>9</td>
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<td>3.5/3.5</td>
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<td>Yes</td>
<td>2+/2+</td>
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<td>Mean</td>
<td>38.6/52.7</td>
<td>2.67/3.0</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*AIMAH indicates corticotropin-independent macronodular adrenal hyperplasia; R, right; L, left; C, compact cells; C1, clear cells; and ellipses, not applicable.
enzymes has been postulated to result in rather ineffective steroidogenesis.\textsuperscript{17} This could logically account for the remarkable size of the nodules and overall adrenal gland weights in most patients with AIMAH. Moreover, the cellular hyperplasia seen in the nodules would be necessary before Cushing syndrome became clinically apparent, which is also in concert with a clinical presentation delayed by a decade or more in mean age beyond that seen for the usual patient with Cushing syndrome. These changes would explain a patient whose only presentation was hypertension, who had no stigmata of Cushing syndrome, but who yet had biochemically and pathologically verified AIMAH after computed tomography serendipitously uncovered the enlarged, nodular adrenal glands.\textsuperscript{16} Although some authors have suggested a minimum size criteria of 50 to 70 g, others believe size alone is not critical.\textsuperscript{10,19} The degree of impairment of steroidogenesis could easily account for size differences in the nodules and adrenal glands, perhaps providing an explanation for the relatively small size of the glands in 3 of our patients whereas all of our patients were found to have nodular cellular hyperplasia. The wide spectrum of symptoms and signs of Cushing syndrome as well as the marked delay in establishing the diagnosis in our patients may be attributable to their impaired and variable steroidogenic machinery. Whereas the biochemical data presented in Table 2 suggest little difficulty in confirming the diagnosis, they belie the often confusing and contradictory data that preceded them, often over many years.

The final line of evidence for a primary intrinsic alteration in the adrenal cells derives from the report by Cheilitin et al.\textsuperscript{20} When cells from a patient with AIMAH were cultured in vitro on an extracellular matrix, they grew rapidly in the absence of ACTH, and they maintained a high rate of cortisol secretion. When the patient's serum was added to cultured fetal adrenal cells, it did not accelerate their growth.

Despite the precise mechanism for the pathogenesis remaining unknown, a much clearer picture of what underlies and helps explain the complex picture of AIMAH has emerged. Sense can now be made of patient’s older age, the difficulty in establishing a diagnosis resulting from a subtle clinical picture for cushingoid features, and biochemical evidence of a primary adrenal source of Cushing syndrome in the face of bilaterally enlarged and nodular adrenal glands. Although empirically patients recovered from their Cushing disease and did not develop Nelson syndrome after bilateral adrenalectomy, the reasons to expect and remain confident of this clinical course are now predicated on solid research. Albeit rare, AIMAH must be considered a separate and legitimate cause of Cushing syndrome.


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REFERENCES


DISCUSSION

Norman W. Thompson, MD, Ann Arbor, Mich: I thoroughly enjoyed this paper, and to back up what Dr Pickleman just said, I will show a slide of a patient I did on Friday of last week showing 2 large adrenal glands on the CT [computed tomographic] scan, each about 12 cm in length. I will show this left adrenal gland that weighed 200 g. The right weighed 200 g. The cut surface is very similar to those that were presented. I show this to give credibility to my comments.

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You have heard what a unique subset of patients have endogenous Cushing's syndrome. We are indebted to Dr Swain and his colleagues for a beautiful, clear presentation. It's also of historical interest that this is probably the smallest series (9 patients) ever to come out of the Mayo Clinic! Furthermore, it took them 18 years to accumulate these cases. You can appreciate the rarity of this entity, 1 patient every 2 years. We have had a similar occurrence. I reviewed our last 12 years' experience with adrenocortical disease and found only 6 patients with this type of macronodular hyperplasia.

Their criteria are quite clear. Ric Lloyd was the pathologist in this series, and he worked with us for 10 years at the University of Michigan. I tried to get him interested in this disease about 6 years ago. I'm not sure about the last point in your criteria, that is, cortical atrophy between the nodules. I haven't had time to review this completely with our current endocrine pathologist yet as I took that picture just before leaving for this meeting. As of yesterday, however, no atrophy was seen between the nodules in this case. My question then to Dr Grant is whether atrophy is an absolutely necessary part of the criteria. It may not exist in every case, particularly when far advanced or with massive adrenals.

Finally, we have heard about the treatment of this unique subset of patients. I believe it does exist and is indeed separate from the pigmented nodular hyperplasia that the Mayo Clinic group has described so well. I'm reminded that 13 years ago at this very location, Dr Aiden Carney was a guest of the Western Surgical Association meeting. During the coffee break I asked him why the Mayo Clinic had never reported any primary hyperplasias. That was 1983, and he proceeded to describe the whole entity we now know as Carney's complex. Two weeks later I saw my first patient with that disease, so it made the entire meeting worthwhile.

The final question I would like to raise is related to the treatment by bilateral adrenalectomy. Is it really necessary to take out both adrenal glands? There have been 5 or 6 patients now described who have had ectopic hormone receptors on the cortical cells in this type of lesion. Three patients had GIP [gastric inhibitory polypeptide] receptors that were food responsive. In other words, every time they ate, the cortisol level shot up. We might call that a Big Mac Attack because of the macronodular hyperplasia!

Last week as a matter of fact, in the New England Journal of Medicine (November 13, 1997), a patient with ectopic β-receptors was described with this type of lesion. He responded to β-blockade with Inderal after a unilateral adrenalectomy. Will we be treating this disease medically in the future? Should all patients be worked up for possible hormone receptor abnormalities before undertaking adrenalectomy?

Richard A. Prinz, MD, Chicago, Ill: In the presentation you mentioned that there have been some cases with a familial predisposition. Were any of the cases in your series in that category? If so, what recommendations do you have for us about screening family members of patients who present with this condition?

Second, in the multiple endocrine neoplasia syndrome where patients develop bilateral pheochromocytomas, we know that they can present initially with just unilateral disease. Did any of your patients present with unilateral disease and then subsequently return with either persistence or recurrence of the syndrome?

Gary B. Talpos, MD, Detroit, Mich: I am impressed with the 7½-year average delay in diagnosis and treatment. What is the corresponding interval in your patients with other forms of hypercortisolism? Secondary hyperparathyroidism is not always corrected by renal transplant. Tertiary hyperparathyroidism results when the precipitating factor of renal failure is removed and parathyroid hypersecretion continues. These parathyroids sometimes exhibit subtle changes both grossly and histologically. In light of your 7½-year delay in treatment, could an analogous situation exist in these patients with regard to their pituitary and adrenal glands? Are you merely operating at a more distant point on the continuum of adrenal disease?

Dr Grant: Dr Thompson asked about our criteria of interstitial adrenocortical atrophy. We rather arbitrarily defined the interstitial cortical atrophy as one of our inclusion criteria so as to help emphasize with as much confidence as possible that these macronodular adrenals were in fact ACTH independent. However, there are patients in the literature, and the one that he showed, who have not demonstrated interstitial atrophy as one of the features. Therefore, this will not be an absolute criteria for other cases in the future.

He also commented about β-adrenergic as well as other cell receptors. We did not test for these in our patients. As he mentioned, there are isolated patients reported who have had GIP, vasopressin, and the single case report that just appeared in the New England Journal of Medicine 6 days ago, with β-adrenergic receptors as a cause of their macronodular Cushing's. Whether eventual treatment long-term with Inderal will be effective is yet to be seen. The recently reported patient from Montreal demonstrated temporary relief of the Cushing's syndrome, but it appeared to be relapsing despite having undergone unilateral adrenalectomy plus the addition of Inderal.

In answer to Dr Prinz, we have not had any patient who has been familiar in our series. Those cases were principally derived from the Japanese literature, and I can't really offer any recommendations about screening. All of our patients had bilateral synchronous adrenal nodular enlargement at presentation. All underwent bilateral adrenalectomies, although others in the literature have reported treatment with unilateral adrenalectomy.

Dr Talpos asks perhaps the most provocative question, that is, the evolution of the pathogenesis. Are these patients just at the very end point of the spectrum, that is, primary ACTH overproduction, eventual hyperplasia and nodule formation, feedback suppression of ACTH, eventual escape from ACTH control and stimulation, and finally autonomous cortisol production by the nodules? In fact, if one extended this concept even further, unilateral single nodules could conceivably evolve in this manner. We do not, however, believe in this pathogenetic mechanism, but it is very difficult to answer absolutely one way or the other.