Isolated Adrenocorticotropic Deficiency Associated with an Autoantibody to a Corticotroph Antigen That Is not Adrenocorticotropic or other Proopiomelanocortin-Derived Peptides*

NICHOLAS P. SAUTER, ROBERTO TONI, CHRISTINE D. MCLAUGHLIN, ERIC M. DYESS, JULIUS KRITZMAN, AND RONALD M. LECHAN

Division of Endocrinology, Department of Medicine, New England Medical Center Hospitals, Boston, Massachusetts 02111

ABSTRACT. A 44-yr-old man with hypocortisolism was shown to have an undetectable basal plasma ACTH level and absent or subnormal ACTH and β-lipotropin responses to provocative testing with insulin, vasopressin, and CRH. Endocrine function after glucocorticoid replacement was otherwise normal, thus establishing the diagnosis of isolated ACTH deficiency. This patient’s serum was tested immunohistochemically for the presence of an antipituitary antibody by indirect immunofluorescence of rat pituitary tissue. Positive immunostaining was observed in stellate-shaped cells in the anterior and intermediate lobes. Immunoreactive cells were shown by immunoelectron microscopy to have ultrastructural characteristics of corticotrophs. Immunoreactivity was concentrated in secretory granules 120–170 nm in diameter. In a double immunolabeling procedure, staining by the patient’s serum was shown to colocalize with rabbit antiserum to ACTH, but not with antisera to FRL, GH, βTSH, or βLH. Immunoabsorption of the patient’s serum with ACTH-(1–24), ACTH-(1–39), γMSH, corticotropin-like intermediate lobe peptide, β-endorphin, or β-lipotropin failed to diminish immunolabeling in the pituitary. We conclude that the antipituitary antibody in this patient’s serum shows immunohistochemical specificity for a rat corticotroph antigen located in secretory granules that is neither ACTH nor any of the proopiomelanocortin (POMC)-derived peptides tested. The autoantigen could be a cell-specific granular factor involved in the posttranslational processing of POMC or secretion of ACTH. We postulate that an autoimmune process may account for this patient’s disease, and that its antipituitary antibody could play a pathogenic role by either inhibiting a POMC-processing enzyme or initiating an antibody-dependent cell-mediated cytotoxicity reaction, resulting in the selective destruction of corticotrophs. (J Clin Endocrinol Metab 70: 1391–1397, 1990)

THE SYNDROME of isolated ACTH deficiency is a very uncommon cause of hypocortisolism (1, 2), with less than 200 cases reported in the literature. Nonetheless, recognition of this disorder is important because it is potentially fatal and easily correctible. The clinical presentation can be similar to that of primary adrenal insufficiency (Addison’s disease), but there is a greater tendency for hypoglycemia (1, 3–6) to occur, and hyperpigmentation is usually absent (1). The diagnosis is established by demonstrating hypocortisolism with undetectable serum levels of ACTH, normal adrenal responsiveness to prolonged ACTH infusion, and an absent ACTH response to insulin-induced hypoglycemia (1). Endocrine function is otherwise normal, with the exception in some cases of reversible hyperthyrotropinemia (7, 8), GH deficiency (9, 10), or hyperprolactinemia (7, 11). Nearly all patients subjected to CRH testing are found to have absent ACTH responses, thus localizing the defect to the pituitary gland (12–16).

Although isolated ACTH deficiency is a heterogeneous disorder with several etiologies reported, including a congenital defect (17), incomplete pituitary infarction associated with pregnancy (18), and hypothalamic damage due to birth trauma (19) or acute intermittent porphyria (20), the majority of cases are most likely due to an autoimmune disorder. This is suggested by the frequent association of isolated ACTH deficiency with other autoimmune conditions, such as type I diabetes mellitus (21, 22), Hashimoto’s thyroiditis (23, 24), Graves’ disease (25), and polyglandular deficiency (26). The reported finding of lymphocytic hypophysitis with a selective absence of corticotrophs in one patient with isolated ACTH deficiency (27) is consistent with an autoimmune process. In addition, antibodies from the serum of patients with this syndrome have recently been found to react

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Address all correspondence and requests for reprints to: Nicholas P. Sauter, M.D., Division of Endocrinology, Box 268, New England Medical Center, 750 Washington Street, Boston, Massachusetts 02111.
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with both rat pituitary tissue (28) and murine At-T-20 (ACTH-secreting) pituitary tumor cells (29).

We have detected an antipituitary antibody in a patient with isolated ACTH deficiency. The purpose of this study was to characterize this antibody immunohistochemically in order to determine its target cell specificity, the ultrastructural localization of the relevant autoantigen, and its possible reactivity with ACTH or other proopiomelanocortin (POMC)-derived peptides.

Case Report

A 44-yr-old male presented with a 6-month history of weight loss (15 kg), fatigue, arthralgias, muscle stiffness, breast enlargement, and forgetfulness. Physical examination revealed postural hypotension (blood pressure, 90/60 mm Hg supine, 80/50 mm Hg upright), a firm thyroid gland, bilateral gynecomastia, and poor short term memory. Pigmentation of the skin and mucosal surfaces was normal, and the testes were normal.

Laboratory evaluation revealed mild anemia (hemoglobin, 123 g/L; normal, 137–173 g/L); serum sodium (138 mmol/L; normal, 135–145 mmol/L), potassium (4.0 mmol/L; normal, 3.5–5.0 mmol/L), and glucose (5.2 mmol/L; normal, 3.3–6.1 mmol/L) levels were normal. Cortisol deficiency with an undetectable basal plasma ACTH level was present (Table 1). GH deficiency was suggested by undetectable basal serum GH and low somatomedin-C determinations; mild hyperprolactinemia was evident. Posterior pituitary function appeared normal by overnight dehydration (Table 2A). After a single iv injection of cosyntropin, a subnormal rise in cortisol was seen, but aldosterone rose normally (Table 2B). After a prolonged iv infusion of ACTH, plasma cortisol and urinary free cortisol rose into or above the normal range (Table 2C). Provocative testing of anterior pituitary function with insulin-induced hypoglycemia and vasopressin resulted in an absent ACTH response and a blunted β-lipotropin (βLPH) response (Table 2, D and E). A severely blunted ACTH response was obtained after the administration of ovine CRH (oCRH; Table 2F). GH responded appropriately to hypoglycemia. Serological tests for antithyroglobulin and antinuclear antibodies were negative; antinuclear antibody was positive, at a titer of 1:320, with a nucleolar pattern. Magnetic resonance imaging (MRI) of the sella turcica was normal.

The patient was treated with prednisone (7.5 mg/day in divided doses). Over the next 3 months, he gained 9 kg weight, his blood pressure rose to 120/80 mm Hg, his weakness, myalgias, and gynecomastia resolved, and his memory impairment improved. The TSH level fell to 5.0 mU/L, and somatomedin-C level rose to 340 U/L.

Table 1. Basal serum hormone levels

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<tr>
<th>Hormone</th>
<th>Patient level</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Morning cortisol (nmol/L)</td>
<td>&lt;2.2</td>
<td>220–660</td>
</tr>
<tr>
<td>ACTH (pmol/L)</td>
<td>&lt;220</td>
<td>2.2–12.0</td>
</tr>
<tr>
<td>T4 (nmol/L)</td>
<td>83.6</td>
<td>54.1–154.0</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>12.0</td>
<td>0.5–5.0</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>&lt;.10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Somatomedin-C (U/L)</td>
<td>200</td>
<td>340–1900</td>
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<tr>
<td>PRL (µg/L)</td>
<td>8.5</td>
<td>0–15</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>12.0</td>
<td>0–20</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>6.4</td>
<td>2–20</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>10.5</td>
<td>10.4–38.1</td>
</tr>
</tbody>
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*ACTH measured in plasma.

Table 2. Provocative endocrine tests

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<tr>
<td>Serum osmolality</td>
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<tr>
<td>Urine osmolality</td>
<td>715 mmol/kg</td>
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<tr>
<td>Cortisol (nmol/L)</td>
<td>25</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)</td>
<td>140</td>
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<table>
<thead>
<tr>
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<tbody>
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<td>ACTH (pmol/L)</td>
<td>30</td>
</tr>
<tr>
<td>p.m. cortisol (nmol/L)</td>
<td>150</td>
</tr>
<tr>
<td>ACTH (pmol/L)</td>
<td>2.2</td>
</tr>
<tr>
<td>PRL (µg/L)</td>
<td>4.0</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>1.0</td>
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</table>

<table>
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<tr>
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<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.5</td>
</tr>
<tr>
<td>ACTH (pmol/L)</td>
<td>&lt;2.2</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>&lt;1.0</td>
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</table>

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>ACTH (pmol/L)</td>
<td>7.0</td>
</tr>
<tr>
<td>p.m. cortisol (nmol/L)</td>
<td>30</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (pmol/L)</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>PRL (µg/L)</td>
<td>6.8</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>1.0</td>
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Materials and Methods

Hormonal assays

Serum concentrations of GH, PRL, somatomedin-C, testosterone, aldosterone, LH, and FSH as well as plasma concent
tions of ACTH and βLPH were determined by competitive, liquid phase RIA. Serum TSH was measured by an immunoradiometric assay. Commercial RIA kits were employed in the following assays: GH, PRL, LH, and FSH (Diagnostic Products, Los Angeles, CA); TSH (Celltech Diagnostics, Ltd., Berkshire, United Kingdom); and testosterone (Radiosystems Laboratories, Carson, CA). ACTH, βLPH, and aldosterone measurements were performed at Nichols Institute (San Juan Capistrano, CA); somatomedin-C was measured at Teterboro Lab (Teterboro, NJ). T 4 and cortisol were determined by a fluorometric enzyme immunoassay (Baxter Healthcare Corp., Miami, FL) on a Stratus analyzer.

**Source of peptides and antisera**

Synthetic ACTH-(1–24), γMSH, corticotropin-like intermediate lobe peptide (CLIP), and β-endorphin were obtained from Bachem, Inc. (Torrance, CA). Synthetic ACTH-(1–39) and natural βLPH (RP-1) were gifts from the National Hormone and Pituitary Program, University of Maryland School of Medicine, and the NIDDK (Award 15553). Rabbit antisera to ACTH was prepared by Leonard P. Kaspar and has previously been well characterized (36); immunocytochemical grade antisera to PRL, GH, βTSH, and βLH were gifts from the Pituitary Hormone Distribution Program of the NIH (Baltimore, MD). Ovine CRH was a generous gift of Dr. George Chrousos, NIH. Informed consent was obtained for the CRH test.

**Indirect immunofluorescence**

Forty-micron vibratome sections of rat pituitary tissue, fixed in Bouin’s solution by intracardiac perfusion, were preincubated in 0.2% Triton X-100 (TX-100; Sigma Chemical Co., St. Louis, MO) in 0.05 M Tris-buffered saline (TBS; pH 7.6) for 20 min and 5% Polyperm (Sigma) in TBS for 30 min at 25 C. Sections were then incubated in either the patient’s or control human serum, obtained from 19 subjects without known autoimmune endocrine disease, diluted 1:100 in 0.3% TX-100 in TBS for 18 h at 4 C. Sections were washed in 0.1 M Sorensen’s phosphate buffer (pH 7.2), incubated in biotinylated antihuman immunoglobulin G (Vector; Vector Laboratories, Burlingame, CA) diluted 1:200 in TBS for 2 h at 25 C, followed by fluorescein-avidin DCS (Vector) diluted 1:250 in TBS for 1 h at 25 C after additional washing. Serial tissue sections were incubated in rabbit anti-ACTH antisera diluted 1:500 in 0.3% TX-100 in TBS, followed by biotinylated antirabbit immunoglobulin (Vector) and fluorescein-avidin DCS.

**Double label immunofluorescence**

In a first immunolabeling step, 40-μm sections of rat anterior pituitary were prepared as described above, using the patient’s serum labeled with fluorescein-avidin DCS. In a second labeling step, sections were incubated for 18 h at 4 C in rabbit anti-ACTH, -βLPH, -PRL, -GH, -βTSH, or -βLH antisera diluted 1:500 in 0.3% TX-100 in TBS. Sections were washed in Sorensen’s phosphate buffer, incubated in biotinylated antirabbit Ig (Vector) diluted 1:200 in TBS for 2 h at 25 C, followed by rhodamine-avidin-D (Vector) diluted 1:250 in TBS for 1 h at 25 C after additional washing.

**Immunosorption Studies**

Forty-micron sections were prepared as described above, except that the patient’s serum was preabsorbed with an excess of ACTH or other POMC peptides for 18 h at 4 C. Peptide concentrations were 10-5 M for ACTH-(1–24), ACTH-(1–39), CLIP, αMSH, γMSH, and β-endorphin and 10-6 M for βLPH. The specificity of rabbit anti-ACTH antiserum was established by demonstrating the absence of immunoreactivity in control sections after preabsorption with 10-5 M ACTH-(1–24) or ACTH-(1–39) for 18 h at 4 C.

**Fluorescence microscopy and qualitative evaluation**

Tissue sections were mounted onto glass slides, overlapped in glycerol-PBS (9:1), and examined under a Zeiss epifluorescent microscope (Zeiss, New York, NY). The green fluorescein isothiocyanate (FITC) fluorescence was examined using a 450- to 490-nm filter set and 520-nm longpass barrier filter, and the red rhodamine fluorescence was examined using a 546-nm bandpass filter and 590-nm longpass barrier filter.

**Immunoelectron microscopy**

Forty-micron sections were prepared as described above, except that the avidin-biotin-peroxidase complex (ABC kit, Vector) was substituted for fluorescein-avidin DCS, and a stable reaction product was developed with diaminobenzidine. Tissue sections were then stained with 1% osmium tetroxide-1.5% potassium ferrocyanide in water for 1 h in the dark at 4 C, followed by 1% uranyl acetate in maleate buffer, pH 6.0, for 1 h in the dark at 4 C, and finally 1% tannic acid in 0.05 M cacodylate buffer, pH 7.4, for 1 h at 25 C (36). Tissue sections were washed in 0.05 M maleate buffer, pH 5.2, for 1 h after each of the first two steps and in cacodylate buffer-1% sodium sulfate for 5 min after the last step. Sections were then dehydrated and flat embedded in Epon 812-Araldite 6005 (1:1) by standard methods (36), cut on an MT 6000 ultramicrotome (RMC, Inc., Tucson, AZ), and examined under a Phillips CM 10 transmission electron microscope (Phillips, Mahwah, NJ).

**Results**

Immunostaining was present in the anterior and intermediate lobes of rat pituitary tissue after incubation with the patient’s serum (Fig. 1A). Immunopositive cells in the anterior pituitary had a stellate appearance, which was similar in both morphology and distribution to that of corticotrophs stained by rabbit anti-ACTH antiserum in serial tissue sections (Fig. 1B). No immunostaining was observed after incubation with normal human control serum (Fig. 1C). By immunoelectron microscopy (Fig. 2), immunopositive cells were characteristically polygonal in shape, contained numerous granules and mitochondria, and were often found adjacent to acidophilic cells. Immunoreactive material was confined to secretory
granules 120–170 nm in diameter. No immunoreactivity was found in association with the plasma membrane or nucleus of immunopositive cells.

To characterize further the immunopositive anterior pituitary cells, double labeling was performed using sera to ACTH and each of the classic anterior pituitary hormones (PRL, GH, βTSH, and βLH). Only ACTH antiserum colocalized with the patient's sera (Fig. 3).

To determine whether antibodies present in the patient's serum recognize either ACTH or a peptide or fragment of its precursor molecule, POMC, immunohistochemical studies were performed with ACTH-(1-39), γMSH, CLIP, β-endorphin, and βLH. No diminution of immunostaining was observed in the patient's serum when preabsorbed with ACTH-(1-39) (Fig. 4A) or any of the other POMC-derived peptides tested. Immunostaining was completely abolished when rabbit anti-ACTH antiserum was preabsorbed with ACTH-(1-24) (Fig. 4B).
Discussion

The endocrine evaluation of the patient described herein was diagnostic for isolated ACTH deficiency. He had hypocortisolism, an undetectable basal plasma ACTH level, normal adrenal responsiveness to a prolonged infusion of ACTH, and absent or severely blunted ACTH and β-LPH responses to provocative anterior pituitary testing with insulin-induced hypoglycemia, vasopressin, and CRH. The results of the CRH test are consistent with a defect at the level of the pituitary, rather than at or above the hypothalamus (13), and are in agreement with reports of CRH testing in other patients with isolated ACTH deficiency (12–16). The glucocorticoid-reversible hyperthyrotropinemia, GH deficiency, gynecomastia, and mental disturbance observed in our patient are findings that have previously been reported in association with isolated ACTH deficiency (9, 10, 37–41). The reversible TSH elevation and GH deficiency most likely represent functional alterations in pituitary secretion due to chronic cortisol deficiency (42–45).

In previously reported cases of isolated ACTH deficiency, the association with other autoimmune endocrine disorders (21–26) and the finding of lymphocytic hypophysitis with a selective loss of corticotrophs (27) have strongly suggested that an autoimmune mechanism underlies this disorder. Our patient showed no evidence of autoimmune thyroid disease by serological testing, but the positive antinuclear antibody test with a nucleolar pattern raises the possibility that he may have an associated subclinical connective tissue disorder, such as progressive systemic sclerosis. Further evidence in support of an autoimmune mechanism in isolated ACTH deficiency comes from reports by Sugiura et al. (28, 29) of antipituitary antibodies in the sera of patients with...
this syndrome. Initially, 10 of 21 patients with isolated ACTH deficiency were shown to have antibodies reacting to rat pituitary tissue, although the specificity of the target cells was not defined (28). Later, it was shown that antibodies from 5 patients with ACTH deficiency reacted to the surface of cells from the murine ACTH-secreting AtT-20 tumor line (29), suggesting specificity of the antibodies for corticotropes.

Using an indirect immunofluorescence method, we have confirmed the observations of Sugiuara et al. (28, 29) by demonstrating the presence of an antipituitary antibody in the serum of our patient with isolated ACTH deficiency. In addition, we have further characterized the antibody through immunoelectron microscopy, double label immunofluorescence, and immunabsorption techniques. The specificity of the patient’s antibody for corticotropes was suggested by thestellate morphology and ultrastructural characteristics of the immunopositive cells (46, 47) and was confirmed by the colocalization of staining by his serum with rabbit antiserum to ACTH, but not with antisera to other anterior pituitary hormones. Restriction of immunopositivity to the secretory granules of anterior pituitary corticotropes raised the possibility that the patient’s autoantibody recognized ACTH or another POMC-derived peptide, but the failure of ACTH or any of the other POMC-derived peptides tested to inhibit pituitary staining after immunoblotting of the patient’s serum suggests that the autoantigen is not any of these molecules. With the exception of γMSH, however, antigenic determinants within the 16-kDa N-terminal fragment of POMC were not specifically tested.

As the relevant autoantigen in our patient is a corticotroph-specific granular factor, we propose two alternative hypotheses to explain his isolated ACTH deficiency. First, the autoantigen may be an enzyme involved in the posttranslational processing of POMC, such as the 70-kDa aspartyl protease recently isolated by Loh et al. (48) from bovine intermediate lobe secretory vesicles. This enzyme, referred to as POMC-converting enzyme, has been shown to cleave POMC in vitro and may be necessary to generate mature ACTH in vivo (48). If this is the case, then isolated ACTH deficiency could have resulted from functional inhibition of the enzyme by antibody binding in a manner analogous to the inhibition of thyroid peroxidase by antimicrosomal antibodies in Hashimoto’s thyroiditis (49). Alternatively, isolated ACTH deficiency may have arisen as a result of selective damage to corticotropes through antibody-dependent cell-mediated cytotoxicity (ADCC) with recruitment of killer (K) cells. This hypothesis is consistent with the autopsy finding of Richtsmeier et al. (27) of lymphocytic hypophysitis with a selective absence of corticotropes in a patient with isolated ACTH deficiency and would be analogous to a second pathogenic action of the thyromicrosomal antibody, destruction of human thyocytes by ADCC, which has been demonstrated in vivo (50).

In summary, using an immunohistochemical approach, we have detected and characterized an antipituitary antibody from the serum of a patient with isolated ACTH deficiency. The antibody reacts specifically with a determinant in the secretory granules of rat anterior pituitary corticotropes. The autoantigen is neither ACTH nor any of several other POMC-derived peptides tested. We speculate that an autoimmune process accounts for the patient’s disease, and that this antipituitary antibody may play a pathogenic role by either inhibiting a POMC processing enzyme or initiating an ADCC reaction resulting in the selective destruction of corticotropes.

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