CASE REPORT

Isolated adrenocorticotropic hormone deficiency due to probable lymphocytic hypophysitis in a man

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ABSTRACT. We report a male patient who presented with severe fasting hypoglycemia in which extensive pituitary and adrenal investigations were diagnostic of isolated ACTH deficiency of pituitary origin. The finding of autoimmune subclinical primary hypothyroidism strongly suggested an autoimmune etiology of the pituitary disease. Lymphocytic hypophysitis, although very rare in male patients, has to be kept in mind when studying patients with pituitary failure of unknown origin, especially when other autoimmune endocrinopathy is present.

INTRODUCTION

Isolated adrenocorticotropic (ACTH) deficiency, defined by low cortisol production with low or normal plasma ACTH levels and no other pituitary abnormalities, is a rare condition that is being recognized with increasing frequency in the last years (1). There are several possible etiologies for this disorder, including autoimmune conditions, and has a wide range of clinical manifestations, from lethargy to overt adrenal crisis.

We present a case of isolated ACTH deficiency associated with subclinical hypothyroidism due to chronic lymphocytic thyroiditis, in an adult male that presented with an episode of severe fasting hypoglycemia. The association with chronic lymphocytic thyroiditis and the absence of any other cause of pituitary failure, gives strong evidence for lymphocytic hypophysitis as etiology of ACTH deficiency in this patient. To our knowledge, only two male patients with lymphocytic hypophysitis have been described previously, and none of them presented with hypoadrenalism (2, 3).

MATERIALS AND METHODS

Methods
Short and long ACTH test, insulin tolerance test (ITT), CRH test, GHRH test, and combined TRH plus LHRH tests were performed in the standard manner (Tables 1 and 2). During 72h-fasting test only noncaloric drinks were allowed, and any food intake was avoided. Samples were taken every 8 h for plasma glucose and insulin measurements, and every 30 min after blood glucose fell below 2.75 mmol/L. Urinary ketones were tested every 8 h. The test was stopped at 48 h as glycemia reached 1.32 mmol/L. At this moment blood samples were taken for determination of plasma insulin, cortisol, GH, pH, bicarbonate (HCO₃⁻), sodium (Na⁺), potassium (K⁺), lactic acid, ammonium, alanine aminotransferase (ALT) and creatinephosphokinase (CPK), and urine was obtained for urinary ketones.

Normal values

The normal peak cortisol following ACTH stimulation, ITT or CRH test was taken to be >500 nmol/L. For both ITT and CRH test a 2-fold increase in ACTH plasma levels was considered an adequate response. Peak plasma GH >326 pmol/L after GHRH or ITT was considered normal. TRH responses were considered adequate with increments equal or greater than 6 mU/L for plasma TSH, and a 2 to 5-fold increase for plasma PRL. The normal range for basal plasma TSH levels was 0.15 to 5.0 mU/L. Basal PRL levels <0.6 nmol/L were considered normal for males less than 40 yr old. Normal plasma LH and FSH were defined by basal values between 4 and 18 U/L for LH and between 2 to 17 U/L for FSH, with at least 2-fold increase in peak values after LHRH. Plasma free T4 levels range from 0.010 to 0.026 nmol/L, and plasma total T3 levels from 1.306 to 2.785 nmol/L. Plasma total testosterone levels range from 10.4 to 34.7 nmol/L.
Table 1 - Tests of hypothalamic-pituitary-adrenal function.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample</th>
<th>-15</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal sampling (after overnight fast)</td>
<td>Plasma cortisol 09:00 (nmol/L)</td>
<td>&lt;55</td>
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<td></td>
<td>Plasma cortisol 21:00 (nmol/L)</td>
<td>&lt;55</td>
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<tr>
<td>Short Synacthen Test (250 µg iv bolus of tetracosactrin)</td>
<td>Plasma cortisol (nmol/L)</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
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<tr>
<td></td>
<td>Plasma ACTH (pmol/L)</td>
<td>2.06</td>
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<tr>
<td>Long Synacthen Test (250 µg iv bolus of tetracosactrin after 1 mg of depot tetracosactrin daily for 3 days)</td>
<td>Plasma cortisol (nmol/L)</td>
<td>88</td>
<td>110</td>
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<tr>
<td>Insulin Tolerance Test (0.075 UI/kg bw iv bolus of regular insulin)</td>
<td>Plasma cortisol (nmol/L)</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
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<tr>
<td></td>
<td>Plasma ACTH (pmol/L)</td>
<td>1.12 0.58 0.52 0.62 0.66 0.54 0.57 0.42</td>
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<tr>
<td></td>
<td>Glycemia (nmol/L)</td>
<td>4.12 4.01 2.42 1.76 2.69 3.02 3.46 3.79</td>
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<tr>
<td>CRH Test (100 µg iv bolus of human CRH)</td>
<td>Plasma cortisol (nmol/L)</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
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<tr>
<td></td>
<td>Plasma ACTH (pmol/L)</td>
<td>2.17 1.27 0.93 1.06 0.85 0.88</td>
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Assays

All patient's samples for each hormone were measured in the same assay. Cortisol was measured by direct RIA (Sorin, Saluggia, Italy) with a sensitivity of 12.5 nmol/L. ACTH was determined by two-site IRMA (Nichols, San Juan Capistrano, CA, USA) with a sensitivity of 0.22 pmol/L. TSH was measured by two-site IRMA (DPC, Los Angeles, CA, USA) with a sensitivity of 0.03 mU/L. Free T4 was measured by analog RIA (DPC, Los Angeles, CA, USA) with a sensitivity <0.0012 nmol/L. Total T3 was determined by direct RIA, with sensitivity 0.107 nmol/L. LH and FSH (CIS, Gil-Sur-Yvette, France), and GH (Nichols), were measured by two-site IRMA, and PRL (Incstar, Stillwater, Minnesota, USA). insulin (Sorin) and testosterone (Sorin) were determined by direct RIAs. Thyroid microsomal and thyroglobulin autoantibodies were determined by semiquantitative agglutination test (Arnes-Miles Inc, Elkhart, IN, USA) and TSH-receptor autoantibodies were measured by inhibition of the binding of 125I-TSH to its receptor (Henning, Berlin, Germany). Pituitary autoantibodies were sought using an indirect immunofluorescent assay, employing snap-frozen monkey pituitary tissue (BioSystem, Barcelona, Spain).

CASE REPORT AND RESULTS

A 27-year-old man presented in the emergency room with prolonged (45 min) loss of consciousness. His parents revealed a history of mild abdominal discomfort, nausea, vomiting and falling, during the last 36 h prior to admission. There were no other significant symptoms and signs. The patient had no previous symptoms of hypothyroidism or other hormonal deficiency, and physical examination, including thyroid palpation, was normal. Initial investigations demonstrate a venous blood

Table 2 - Tests of pituitary function.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample</th>
<th>-15</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal sampling</td>
<td>Total Testosterone (nmol/L)</td>
<td>13.5</td>
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<tr>
<td>Insulin Tolerance Test</td>
<td>Plasma GH (pmol/L)</td>
<td>&lt;27.9 &lt;27.9 &lt;27.9 &lt;27.9 297 390 153 65</td>
<td></td>
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<tr>
<td>GHHR Test (1µg/kg bw iv)</td>
<td>Plasma GH (pmol/L)</td>
<td>&lt;27.9 520 804 958 916 520 279</td>
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</tr>
<tr>
<td>Combined TRH (400 µg iv) + LHRH (100 µg iv) Test</td>
<td>TSH (mU/L)</td>
<td>26.4 22.4 33.1 32.5 34.1</td>
<td></td>
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<tr>
<td></td>
<td>PRL (nmol/L)</td>
<td>0.9 0.6 1.6 1.5 0.9</td>
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<tr>
<td></td>
<td>LH (IU/L)</td>
<td>22.2 19.4 70.7 116.5 127.0</td>
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<tr>
<td></td>
<td>FSH (IU/L)</td>
<td>8.5 6.6 11.5 14.9 17.7</td>
<td></td>
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</tbody>
</table>
glucose of 1.87 mmol/l. He was immediately treated with intravenous infusion of hypertonic glucose solution (20 ml of 50% dextrose solution) with complete recovery of consciousness and abdominal symptoms.

The patient was placed on a normal 2,000 kcal per day diet and a short 1-24 ACTH (Synacthen) test was performed. After 4 days with normal blood glucose values, and whilst awaiting for the results of ACTH test, a 72 h fasting test was performed, showing symptomatic hypoglycemia at 48 h with venous blood glucose levels of 1.32 mmol/l. Simultaneous plasma insulin levels were low (51.66 pmol/l) and plasma cortisol was undetectable (<55 nmol/l). During hypoglycemia venous pH was low (7.24), and plasma levels of GH (683.5 pmol/l), lactate acid (0.7 mmol/l), ammonium (32.13) µmol/l), ALAT (38 U/L) and CPK (126 U/L) were all in the normal range. Plasma insulin levels were under the sensitivity of the assay for all blood glucose levels except during profound hypoglycemia, and ketonurias were negative all along the fasting test.

The short and long 1-24 ACTH test were diagnostic of adrenocortical insufficiency, with basal and stimulated plasma cortisol levels under the sensitivity of the assay. Basal plasma ACTH levels were also low demonstrating the secondary origin of adrenocortical failure. Na+ and K+ were normal. An ITT and a CRH test were then performed, showing no ACTH and cortisol response. The results of the tests of hypothalamic-pituitary-adrenal function are listed in Table 1. A magnetic resonance of the sella showed a normal pituitary gland. After beginning hydrocortisone replacement therapy (20 mg at 09:00 and 10 mg at 18:00) the patient underwent extensive pituitary investigations (Table 2) that ruled out other pituitary abnormalities. Surprisingly, the patient's thyroid function was abnormal with low-normal plasma levels of thyroid hormones (Table 3) and moderately elevated levels of basal and stimulated TSH (Tables 2 and 3), indicating primary subclinical hypothyroidism. Thyroid autoantibodies were positive (Table 3) suggesting an autoimmune etiology. TSH-binding inhibiting immunoglobulins (TBI) were absent. Pituitary and adrenal autoantibodies were negative. The diagnosis of chronic lymphocytic thyroiditis (atrophic variant) was made. After one month with hydrocortisone replacement therapy, basal plasma TSH decreased to minimally elevated levels with normal T3 and T4 (Table 3), although the patient was not placed on thyroid replacement. Thyroid function was reevaluated after 6 months on hydrocortisone, showing minimally elevated TSH levels, normal thyroid hormone values and marked decrease in thyroid autoantibodies (Table 3). The patient is actually on replacement therapy with hydrocortisone only, without any symptoms or signs of endocrine dysfunction.

**DISCUSSION**

Isolated ACTH deficiency is an uncommon disease, with a wide spectrum of presentation. Symptoms are usually insidious, and diagnosis requires a high grade of suspicion. Hypoglycemia, alone or in combination with postural hypotension or hypotensionia, has been described as presenting symptom in some patients (1, 4), but patients' symptoms can range from mild asthenia to overt adrenal crisis. The etiology of this entity is uncertain in most cases. Several associated conditions have been described, such as empty sella turcica (1, 5), benign intracranial hypertension (6) and cranial traumatism (7). An autoimmune etiology has also been suggested, such this condition has been reported in association with lymphocytic hypophysitis (8, 9) or other autoimmune diseases like insulin-dependent diabetes mellitus (IDDM) (10) or postpartum thyroiditis (9). Isolated ACTH deficiency may be accompanied by other hormonal abnormalities, that can resolve or improve with steroid replacement therapy. Reversible abnormalities include hypotestosteronemia (1), anovulation (11), gyneco-

<table>
<thead>
<tr>
<th>Sample</th>
<th>At diagnosis</th>
<th>At 1 month</th>
<th>At 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free T4 (nmol/L)</td>
<td>0.01</td>
<td>0.022</td>
<td>0.016</td>
</tr>
<tr>
<td>Total T3 (nmol/l)</td>
<td>1.82</td>
<td>1.92</td>
<td>2.20</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>26.38</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Microsomal auto-ab. title</td>
<td>1/6400</td>
<td>-</td>
<td>1/1600</td>
</tr>
<tr>
<td>Thyroglobulin auto-ab. title</td>
<td>1/10240</td>
<td>-</td>
<td>1/160</td>
</tr>
<tr>
<td>TBI (U/L)</td>
<td>0</td>
<td>-</td>
<td>2</td>
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</tbody>
</table>
mastia (12), hyperprolactinemia (13) and GH insufficiency (14). An improvement in glycemnic control in a patient with IDDM after initiation of corticosteroid replacement therapy has also been reported (10).

In our patient, the lack of response of plasma cortisol to short and long Synacthen® test, and to insulin-induced hypoglycemia, clearly showed adrenal insufficiency. This evidence was also supported by the undetectable plasma cortisol levels observed during the profound hypoglycemia induced by prolonged fasting test. Secondary hypoadrenalinism was confirmed by the finding of low plasma ACTH with simultaneous undetectable plasma cortisol values, and lack of ACTH response to insulin-induced hypoglycemia. Secondary adrenal insufficiency could represent ACTH or CRH failure, depending on the location of the lesion.

In the present case the lack of plasma ACTH response to exogenous CRH suggests pituitary origin of ACTH deficiency. In the present case, the association with chronic lymphocytic thyroiditis strongly suggest lymphocytic hypophysitis as the etiological mechanism of the isolated ACTH deficiency (15), moreover no other causes of secondary hypoadrenalinism were present. Lymphocytic hypophysitis usually occurs in women presenting with headaches, optic pathway involvement, pituitary mass and positive pituitary autoantibodies. However, it has been reported in two male patients (2, 3), and lack of some of these typical findings has also been described in several cases (16). Lymphocytic hypophysitis has been reported in association with autoimmune thyroid disease, mainly postpartum thyroiditis, but also with several autoimmune disorders like adrenalinitis, atrophic gastritis and pernicious anemia, parathyroiditis, Schmidt’s syndrome and retroperitoneal fibrosis (16). The association with chronic lymphocytic thyroiditis, whose ultrastructural changes are identical to those seen in lymphocytic hypophysitis (16), is also favored by the finding that in patients with lymphocytic hypophysitis in which HLA class III alleles have been ascertained, the complement allotype was identical in all of them, and was a complement associated with Hashimoto’s thyroiditis (3, 17). The absence of pituitary autoantibodies in our patient does not necessarily argues against autoimmune hypophysitis. In several patients with biopsy-proven autoimmune hypophysitis pituitary autoantibodies were not detected, and the presence of such autoantibodies is not specific of pituitary autoimmunity, as has been described in patients with Cushing’s disease or empty sella turcica (9). The definitive diagnosis of lymphocytic hypophysitis rests on pituitary biopsy, that could not be performed in our patient asellar magnetic resonance disclosed a normal pituitary gland.

In our patient, the normalization of plasma TSH levels after hydrocortisone replacement could represent a reduction in TSH hypersecretion, as has been reported with hyperprolactinemia in other cases of ACTH deficiency (13) and occasionally in Addison’s disease (18). Another possibility is amelioration of thyroid autoimmune damage, as a marked decrement in thyroid autoantibodies was observed. A possible role of TSH-receptor blocking antibodies in the changes in thyroid function parameters observed in our patient has been ruled out, since serum TBII were normal at diagnosis and after 6 months of steroid replacement therapy (Table 3).

In our opinion, this case presents several remarkable aspects. First, the presence of lymphocytic hypophysitis in male patients has only been previously described in two cases, in whom it was associated neither with isolated ACTH deficiency nor with other autoimmune endocrinopathies (2, 3). Second, the reversibility of primary thyroid failure after hydrocortisone replacement alone has not been described previously. This points to the need of a close follow-up after the initiation of glucocorticoid replacement therapy before placing the patient on hormonal substitution for specific deficiencies, that might be reversible. Finally, this extremely rare association expands the possibilities of coexistence of autoimmune endocrinopathies, and has to be kept in mind when studying a patient with thyroid and adrenocortical failure.

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