Reversible Adrenocorticotropic Deficiency due to Probable Autoimmune Hypophysitis in a Woman with Postpartum Thyroiditis

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ABSTRACT. The natural history and pathogenesis of lymphocytic hypophysitis remain poorly understood. We describe a 34-yr-old woman with postpartum thyroiditis and ACTH deficiency, studied at monthly intervals for 18 months after pregnancy. A significant titer of thyroid peroxidase autoantibodies was detected at 16 weeks gestation, and she was recruited into a prospective study of postpartum thyroid function. Four months postpartum she developed mild hyperthyroidism [free T₄ (fT₄), 27 pmol/L; TSH, <0.2 mU/L] and showed a rise in thyroid peroxidase and thyroglobulin autoantibodies. At 9 months postpartum, serum fT₃ and T₃ levels were low normal (8.0 and 1.7 pmol/L, respectively), but TSH was not raised (0.4 mU/L). Subsequent investigation showed a low basal plasma cortisol level (28 nmol/L) in association with undetectable ACTH, and subnormal cortisol responses to depot Synacthen (535 nmol/L at 6 h) and hypoglycemia (peak, 145 nmol/L). FSH, LH, GH, and PRL function and computerized tomography of the pituitary were normal. Retrospective analysis of serum samples taken throughout the postpartum year showed developing hypocortisolism between 3–9 months postpartum. Each sample was also tested for pituitary autoantibodies using a specific indirect immunofluorescent assay; none was detected. The ACTH deficiency recovered spontaneously, with normal cortisol responses to depot Synacthen (>1380 at 6 h) and hypoglycemia (peak, 590) 14 and 18 months postpartum, respectively. This case illustrates that postpartum pituitary deficiencies are potentially reversible. The pattern of pituitary deficit and postpartum thyroiditis supported a diagnosis of autoimmune hypophysitis. (J Clin Endocrinol Metab 74: 548–552, 1992)

DURING the past decade, lymphocytic hypophysitis has been recognized increasingly as a cause of hypopituitarism, although its precise incidence remains unclear. It occurs particularly in women during late pregnancy and the postpartum period (1, 2), and only two men with the condition have been described (2, 3). There is a spectrum of presentation. At one extreme, patients may present with symptoms of an expanding pituitary mass and require surgical decompression, which enables histological confirmation of the diagnosis. At the other, patients may present with varying degrees of pituitary hypofunction and have normal radiology. In the latter, the pattern of pituitary failure and the presence of concomitant autoimmune endocrine disease may suggest lymphocytic hypophysitis, but in the absence of a pituitary biopsy, the diagnosis cannot be proved conclusively. We describe a 34-yr-old woman who attended our thyroid research clinic at monthly intervals after pregnancy and provided a unique opportunity to study the time course and reversibility of postpartum pituitary hormone deficiencies, particularly ACTH.

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Materials and Methods

Free T₄ (fT₄) and T₃ were measured by analog RIA (Amerlex-M, Amersham International PLC, Aylesbury, Buckinghamshire, United Kingdom), with interassay coefficients of variation of 4.5% and 3.3% at serum concentrations of 12.7 and 3.4 pmol/L, respectively. Our in-house two-site immunoradiometric assay for TSH has a detection limit of 0.2 mU/L and an interassay coefficient of variation (cv) less than 10% between concentrations of 0.5–60 mU/L. Cortisol was evaluated by direct RIA, with a sensitivity of 28 nmol/L and an interassay cv of 7% at 440 nmol/L (4). ACTH was determined by N-terminal-specific RIA, with a sensitivity of 2.2 pmol/L (10 mL plasma extraction) and an interassay cv of 8% at 11 pmol/L (5). FSH and LH were measured by RIA, and GH and PRL by two-site immunoradiometric assay, all with an interassay cv below 10%. Thyroid peroxidase (TPO) and thyroglobulin (Tg) autoantibodies were quantified by enzyme-linked immunosorbent assay (6), and TSH receptor antibodies by RRA (7). Pituitary autoantibodies were sought using an indirect immunofluorescent assay, employing snap-frozen human fetal pituitary tissue (8). HLA typing was performed as previously described (9).

Case Report

A 34-yr-old Welsh woman delivered her second child at term in March 1989. The pregnancy had been uneventful, without
pregnancy hypertension or episodes of severe headache, and the delivery was uncomplicated. Thyroid disease was not suspected clinically, but screening at 16 weeks gestation had revealed a significant level of TPO autoantibodies (1230 U/mL; normal, <525), and she was recruited into the Caerphilly Pregnancy Thyroid Survey, an ongoing prospective study of postpartum thyroid dysfunction involving monthly assessment after delivery for a period of 1 yr. She had previously enjoyed good health and was taking no medication. There had been one previous normal pregnancy in 1986, and a 12-week spontaneous abortion in April 1988.

Breastfeeding was established easily after her third pregnancy and continued for 9 months, and her regular 28-day menstrual cycle resumed 6 months postpartum. She noted temporary loss of axillary hair 3 months after delivery. Four months postpartum she developed symptoms consistent with mild hyperthyroidism (anxiety, slight tremor, heat intolerance, and a few pounds weight loss), but these resolved within 1 month. At this time she had slightly raised serum free T3 (27 pmol/L), undetectable serum TSH (<0.2 mU/L), and increased TPO autoantibodies (peak, 8040 U/mL; Fig. 1). A radioiodine uptake scan could not be performed to confirm destructive thyroiditis because she was breastfeeding. However, the transient hyperthyroidism and absence of TSH receptor antibodies made Graves' disease unlikely. Between 6 and 9 months postpartum, free T4 levels were at the lower limit of normal, and T3 levels were subnormal, but TSH concentrations remained within the normal euthyroid range (Fig. 1). The latter observation raised the possibility of pituitary dysfunction, and cortisol was undetectable (<28 nmol/L) in a midafternoon plasma sample taken 9 months postpartum.

At this time, she was entirely well and had no symptoms to suggest glucocorticoid deficiency. There were no abnormal findings on clinical examination; she was not pigmented, blood pressure was 106/66 mm Hg with no postural fall, and she had normal body hair. She underwent detailed endocrine investigation, the results of which are shown in Table 1. Cortisol deficiency was shown clearly by both insulin-induced hypoglycemia and depot Synacthen tests. Secondary hypoadrenalism was confirmed by the finding of undetectable ACTH in a snap-frozen plasma sample taken at 0900 h, at which time plasma cortisol was 28 nmol/L. Normal serum Na+ (139 mmol/L) and K+ (4.1 mmol/L) provided further evidence against primary adrenocortical failure. The serum TSH concentration was not raised in the presence of low free thyroid hormone concentrations, although there was a normal increase after TRH administration. In contrast, basal concentrations of FSH, LH, GH, and PRL were normal, and there were normal responses to appropriate stimuli. High resolution computerized tomography of the hypothalamus and pituitary (Phillips TX scanner) showed a normal-sized pituitary, with no mass lesion. Apart from TPO antibodies, which remained positive, organ-specific antibodies were negative by indirect immunofluorescence, including adrenal and anterior pituitary.

Despite her lack of symptoms, she was advised to take replacement hydrocortisone, but she stopped treatment after just a few days. Retrospective analysis of midafternoon serum samples stored from her monthly visits to the research clinic showed a gradual decline in cortisol concentrations between 3 and 6 months postpartum, reaching undetectable levels at around 9 months (Fig. 1). No pituitary autoantibodies were detected in the same samples at any time during the postpartum year. Depot Synacthen testing was repeated at 11 months and showed a subnormal response similar to that at 9 months, although basal cortisol at 0900 h had risen to 140 nmol/L (Fig. 2A). However, normal hypothalamo-pituitary-adrenal function had returned a few months later, as demonstrated by entirely normal 0900 h plasma cortisol concentrations and responses to depot Synacthen (at 14 months; Fig. 2A) and insulin-induced hypoglycemia (at 18 months; Fig. 2B). At 18 months, plasma ACTH at 0900 h was 3.3 pmol/L (normal range, 2.2–17.6), and cortisol was 450 nmol/L.

Her detailed HLA phenotype was as follows: class I and II alleles HLA-A3, A29; B7, B44; Bw4, Bw6; DR16, DR7; DQw53; DQw6, DQw2; class III (complement) alleles Bf, BfS, C4A3, C4B1, Gm phenotype Gm 1, 2, 3, 17; - - 5, 11, 21 and Km phenotype Km1, Km3.

**Discussion**

There was no clinical indication for our patient to have a pituitary biopsy, but even in the absence of definitive histology, we consider that there is strong evidence for autoimmune hypophysitis. The main etiologies in the differential diagnosis of ACTH deficiency in a postpartum woman are Sheehan's syndrome, pituitary tumor,
and lymphocytic hypophysitis. Sheehan's syndrome was improbable, since the pregnancy and delivery were completely unremarkable from the obstetrical viewpoint. Furthermore, breastfeeding and resumption of menses were achieved without difficulty or delay. Pituitary microadenomas may occur in patients with normal high resolution computerized tomography of the pituitary, but major endocrine deficiency in this situation is virtually unknown. The pattern of pituitary deficiency was also against a diagnosis of pituitary adenoma; in tumor patients, GH and gonadotropin levels are generally reduced first, followed later by ACTH and TSH deficiency. In fact, the pattern of endocrine loss in our patient is characteristic of lymphocytic hypophysitis. Five women have been described with a pituitary mass due to lymphocytic hypophysitis, and hypothyroidism and hyperandrogenism without hypogonadism (1, 10–13). GH secretion in such patients is also usually normal (1). Other cases of postpartum hypopituitarism have been described who were not biopsied and had pituitary deficiencies out of proportion to their minimal anatomical abnormalities, as in our patient (1). The close temporal relationship of the hypopituitarism to the well documented episode of postpartum thyroiditis in our patient provides strong circumstantial evidence for a common autoimmune etiology.

The significance of the presence or absence of serum pituitary autoantibodies in this situation remains unclear. Of 7 cases of biopsy-proven lymphocytic hypophysitis tested for pituitary antibodies using a variety of assays (2, 10, 14–17), 5 were negative. Furthermore, pituitary antibodies were found in only 1 of 2 cases of idiopathic hypopituitarism in whom no biopsy was performed (18, 19). All of the above were measured in single serum samples, and in order to explain the negative results, it has been speculated that antibody titers might fluctuate throughout the course of the disease, as in postpartum thyroiditis. However, our patient did not have pituitary autoantibodies at any time during the postpartum year and is unique in that serial samples were tested. The antibody assay employing fresh human fetal pituitary tissue has been used recently to demonstrate antibodies to pituitary corticotrophs in sera from 13 of 51 patients with Cushing's disease (8). Pouplard et al. (20) showed that adult human corticotrophs express Fc receptors and, thus, exhibit a nonantibody-specific affinity for human immunoglobulins; such receptors are absent in fetal corticotrophs, which should provide a more specific substrate for antibody testing (8). Pituitary antibodies have also been demonstrated in normal postpartum women (21), patients with autoimmune polyglandular endocrine syndromes (22), and women with empty sella syndrome (23). Their significance in these conditions and the role of humoral immunity in the pathogenesis of lymphocytic hypophysitis remain unclear.

Only five previously described cases of lymphocytic hypophysitis have been tissue typed (2, 3, 10, 24); our patient shared one class I (Bw4) and two class II alleles. 

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**TABLE 1. Endocrine investigations 9 months postpartum**

<table>
<thead>
<tr>
<th>Normal range or response</th>
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**Depot Synacthen (1 mg, im)**

<table>
<thead>
<tr>
<th></th>
<th>0 h</th>
<th>6 h</th>
<th>8 h</th>
<th>24 h</th>
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</thead>
<tbody>
<tr>
<td>Cortisol (nmol/L)</td>
<td>28</td>
<td>535</td>
<td>690</td>
<td>408</td>
</tr>
<tr>
<td>ACTH (pmol/L)</td>
<td>&lt;2.4</td>
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**LHRH (100 µg, iv)**

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<th></th>
<th>0 min</th>
<th>20 min</th>
<th>60 min</th>
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<tbody>
<tr>
<td>LH (IU/L)</td>
<td>4.3</td>
<td>26.1</td>
<td>37.9</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>2.5</td>
<td>6.4</td>
<td>9.8</td>
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5 x basal at 20 min
2 x basal at 20 min

**TRH (200 µg, iv)**

<table>
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<th></th>
<th>0 min</th>
<th>20 min</th>
<th>60 min</th>
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<tbody>
<tr>
<td>TSH (mU/L)</td>
<td>0.4</td>
<td>13.0</td>
<td>10.9</td>
</tr>
<tr>
<td>PRL (mU/L)</td>
<td>194</td>
<td>2260</td>
<td>1160</td>
</tr>
<tr>
<td>fT4 (pmol/L)</td>
<td>8.0</td>
<td></td>
<td></td>
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<tr>
<td>fT3 (pmol/L)</td>
<td>1.7</td>
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2-8 x basal at 20 min
peak >5 x basal
9-26
3-9

**Insulin-induced hypoglycemia (0.05 U/kg, iv)**

<table>
<thead>
<tr>
<th></th>
<th>0 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
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<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.4</td>
<td>1.4</td>
<td>3.1</td>
<td>3.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>50</td>
<td>&lt;28</td>
<td>145</td>
<td>55</td>
<td>&lt;28</td>
</tr>
<tr>
<td>GH (mU/L)</td>
<td>6.8</td>
<td>28.4</td>
<td>30</td>
<td>18.8</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Peak >500
Peak >20
(DR7 and DQw2) with one of these patients (Ref. 2, patient 1), but did not possess the A1-B8-DR3 combination found by some researchers to occur with increased frequency in patients with postpartum thyroiditis (9). However, it is of particular interest that her class III complement allotype was identical to that found in the two patients with lymphocytic hypophysitis in whom it has been ascertained (2) and that this is a complementotype associated with Hashimoto’s thyroiditis (25).

The incidence of postpartum autoimmune hypophysitis is unknown. We have reviewed the postpartum thyroid profiles of 148 TPO autoantibody-positive women in the Caerphilly Pregnancy Thyroid Survey, 73 of whom developed postpartum thyroiditis, as defined by Othman (26), and none showed the pattern observed in the present case. This suggests that less than 1% of patients with postpartum thyroiditis develop postpartum hypophysitis, but this figure should be interpreted with caution, since we have not conducted prospective studies of pituitary function in these patients.

The long term outcome of untreated lymphocytic hypophysitis is poorly defined, and in patients with mass lesions may be altered by surgical intervention. McGrail et al. (12) described a 27-yr-old woman with well documented ACTH, TSH, and PRL deficiency during pregnancy which had completely recovered 1 yr after surgical decompression. Many more, however, have had permanent endocrine deficits after surgery (1). The long term endocrine outcome in patients with probable lymphocytic hypophysitis who were not biopsied is unknown. The present report suggests that some deficiencies may be reversible, and it would seem prudent to withdraw pituitary substitution therapy for repeat endocrine assessment at 1 yr postpartum.

Acknowledgments

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References


