Autoimmune Hypophysitis
Shereen Ezzat and Robert G. Josse

Autoimmune (lymphocytic) hypophysitis has emerged as a distinct and specific clinical and pathological disease entity. Although relatively rare compared with other autoimmune endocrine diseases, nearly a hundred cases have been described. The condition is much more common in females (9:1) and appears to have a particular predilection for the pregnant and postpartum states. The anterior pituitary, and less often the neurohypophysis, appear to be the target for inflammatory autoimmune destruction. During the evolution of the disease process, pituitary hyperfunction (usually hyperprolactinemia) has been noted. This disease should now be included in the differential diagnosis of pituitary disorders, especially in females presenting with pituitary enlargement, particularly if symptoms occur in temporal relationship to pregnancy. The disease may form part of the spectrum of the polyglandular autoimmune endocrine disorders. (Trends Endocrinol Metab 1997;8:74–80). © 1997, Elsevier Science Inc.

Many endocrine glands, either singly or in combination, are subject to autoimmune injury. The basic mechanisms underlying the endocrine dysfunction are thought to result from similar aberrations of the immune system. Lymphocytic hypophysitis, a relatively rare example of autoimmune endocrine disease, was first described in 1962 (Goudie and Pinkerton 1962). Since that time, nearly a hundred cases have been reported. The condition may be more prevalent, and although there are a few distinctive clinical clues, there are currently no laboratory markers and definitive diagnosis without surgical biopsy has been problematic. The condition has been linked with several other autoimmune endocrine disorders (Thodou et al. 1995, Asa et al. 1981, Pholsena et al. 1994, Ozawa and Shishiba 1993, Bevan et al. 1992, Josse 1990). Lymphocytic hypophysitis may have an acute onset and occasionally results in severe complications, even a lethal outcome. In addition, the clinical and radiographic presenting features may simulate those of a pituitary adenoma. The diagnosis has been most commonly confirmed by histologic examination. In many endocrine autoimmune diseases, serum autoantibodies act as serological markers of disease; however, antipituitary antibody measurement is difficult to perform and not routinely available. Moreover, it remains unclear whether the pituitary antibodies have any real diagnostic or predictive value, as there is still no definite correlation between the presence of
pituitary antibodies and corresponding pituitary hormone deficiency.

In this review, the clinical, biochemical, radiographic, and morphological features of lymphocytic adenohypophysitis are presented. The clinical outcome and response to treatment are discussed, and management guidelines are proposed for an approach to this condition.

- Clinical Presentation

Patient Profile

From review of the literature of the first 100 patients, nearly 85% of subjects affected were females. The mean age at presentation was approximately 30 years compared with 40 years in males. At least two thirds of cases have been associated with pregnancy, nearly half presenting during the second or third trimester and the other half during the first 6 months postpartum (Asa et al. 1981, Thodou et al. 1995, Josse 1990).

Symptoms

The clinical presentation of patients with lymphocytic hypophysitis involves two categories of symptoms. Those resulting from mass effects such as headache and visual field impairment have been reported in nearly 60% of patients (Asa et al. 1981, Supler and Mickle 1992, Nussbaum et al. 1991, Stelmach and O’Day 1991, Ludmerer and Kissane 1993, Lee et al. 1994, Scully et al. 1995, Thodou et al. 1995). Double vision arising from extension of the inflammatory mass into the cavernous sinuses has been noted in 6% of patients with lymphocytic hypophysitis (Supler and Mickle 1992, Nussbaum et al. 1991).

Hyperprolactinemia

Hyperprolactinemia is a feature in nearly 40% of patients with lymphocytic hypophysitis (Asa et al. 1981, Ober and Elster 1994, Pestell et al. 1990, Parent 1990, Thodou et al. 1995). Although PRL hypersecretion is a physiologic feature of pregnancy and the postpartum period, this observation only partially explains the PRL excess noted in this condition. Indeed, lactotroph hyperplasia demonstrated by electron microscopy in some patients may represent an alternative explanation (Thodou et al. 1995); however, of the nearly 20 cases in the literature with reported hyperprolactinemia, several have been in males (Puchner et al. 1994, Guay et al. 1987, Supler and Mickle 1992, Lee et al. 1994, Thodou et al. 1995), and at least half were females who were not pregnant or breast feeding at the time of diagnosis (Portocarrero et al. 1981, McCutcheon and Oldfield 1991, McConnon et al. 1991, Nussbaum et al. 1991, Masana et al. 1990, Ludmerer and Kissane 1993). In many of these pa-

Figure 1. Computed tomographic appearance of the pituitary in lymphocytic hypophysitis. This view of the sella in a 24-year-old female presenting with a visual field defect and hyperprolactinemia postpartum reveals an enlarged pituitary with domelike suprasellar extension mimicking a pituitary adenoma.

Figure 2. Light microscopic features of the anterior pituitary in lymphocytic hypophysitis. In this lesion, adenohypophysial tissue and its architecture are still recognizable. Original magnification ×250.
tients, elevated PRL levels may represent an endocrine marker of the disease. Several suggestions have been proposed. Stalk compression resulting in reduced dopamine delivery to the anterior pituitary (stalk phenomenon) represents a possibility. This theory most likely accounts for hyperprolactinemia associated with suprasellar masses. Alternatively, the inflammatory process may directly alter dopaminergic receptors and the inhibitory effect of dopamine on PRL release. An autoimmune mechanism involving the production of stimulating antibodies by plasma cells may lead to increased hormone secretion, analogous to the pathophysiological mechanisms implicated in Graves' disease of the thyroid. Finally, diffuse destruction by the inflammatory process may, in some cases, result in escape of hormone into the systemic circulation.

These latter possibilities may account for PRL hypersecretion in some patients and, possibly, the GH or GH and PRL excess documented in others (Hughes et al. 1993, Thodou et al. 1995).

**Anterior Pituitary Insufficiency**

Symptoms resulting from partial or complete anterior hypopituitarism are noted in 65% of patients (Festell et al. 1990, Guay et al. 1987, Cosman et al. 1989, Puchner et al. 1994, Lee et al. 1994, Thodou et al. 1995).

Selective loss of adenohypophysial cells is likely to be the result of a targeted autoimmune attack. The absence of corticotrophs histologically correlates well with the clinical presentation of cortisol deficiency. This finding is often based on biopsy specimens and, therefore, needs to be interpreted with caution, as it may not indicate total absence of corticotrophs from the entire pituitary. Even though isolated ACTH deficiency is rare, it represents the most common isolated type of anterior pituitary-hormone deficiency encountered in patients with proven or suspected lymphocytic hypophysitis (Sauter et al. 1990, Richtsmeier et al. 1980, Escobar-Morreale et al. 1994, Bevan et al. 1992, Gal et al. 1986). Isolated TSH or gonadotropin deficiency has also been described (Barkan et al. 1985).

**Diabetes Insipidus**

Neurohypophysial involvement manifesting as diabetes insipidus is encountered in 20% of patients (Paja et al. 1994, Ludmerer and Kissane 1993, Koshiyama et al. 1994, Thodou et al. 1995). Neurohypophysial dysfunction may be attributed to direct inflammatory invasion, destruction, and/or compression of either the posterior lobe or pituitary stalk.

**Associated Autoimmune Conditions**

A review of previously published reports indicates that nearly 20% of patients present with a history of other autoimmune conditions. Among these, primary hypothyroidism secondary to chronic lymphocytic thyroiditis represents the most common finding. A similar frequency of 25% was identified in our recent series (Thodou et al. 1995). In addition, transient lymphocytic thyroiditis (Bevan et al. 1992, Ozawa and Shishiba 1993), parathyroiditis, adrenalitis, atrophic gastritis (Pholsena et al. 1994, Asa et al. 1981, Roosens et al. 1982), and autoimmune polyglanulard failure have also been reported (Barkan et al. 1985, Kojima et al. 1982). Other endocrinological findings included hypercalcemia in a minority of patients. Although this has occasionally been associated with parathyroid hyperplasia (Thodou et al. 1995), it is more commonly attributed to coexisting hypocortisolism.

**Radiographic Features**

Computed tomography (CT) or magnetic resonance (MR) imaging reveals pituitary enlargement or a sellar mass similar to a pituitary tumor in almost 80% of cases (Figure 1). In many instances, suprasellar extension cannot be easily distinguished from a pituitary adenoma. Recent reports, however, point to some possible unusual features that may be more specific to hypophysitis.

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**Table 1. Clinical features of lymphocytic hypophysitis**

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<tr>
<th>Finding</th>
<th>Frequency&lt;sup&gt;a&lt;/sup&gt; (%)</th>
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<tr>
<td>Female gender</td>
<td>90</td>
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<tr>
<td>Clinical mass effects</td>
<td>60</td>
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<tr>
<td>(Headache, visual field defect)</td>
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<tr>
<td>Hyperprolactinemia</td>
<td>40</td>
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<tr>
<td>Pituitary insufficiency</td>
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<tr>
<td>Anterior</td>
<td>65</td>
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<tr>
<td>Diabetes insipidus</td>
<td>20</td>
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<tr>
<td>Pituitary enlargement</td>
<td>80</td>
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<tr>
<td>Associated autoimmune disease</td>
<td>25</td>
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<sup>a</sup> Data based on findings derived from 100 case reports, as described in the main text.
These include loss of the hyperintense "bright spot" signal of the normal posterior pituitary on sagittal views, thickening of the pituitary stalk, and actual enlargement of the posterior pituitary (Imura et al. 1993, Abe et al. 1995). These radiographic features, however, still require prospective validation. Occasionally, only a stalk lesion can be detected, whereas in others the examination may be unremarkable.

- Pathological Features

The histologic features of autoimmune hypophysitis appear to be fairly uniform (Figures 2 and 3). Grossly, the gland may be enlarged or atrophic. This may represent, as in other autoimmune endocrinopathies, a spectrum of disease from diffuse enlargement with inflammatory infiltrate to an atrophic fibrotic gland.

Light microscopy shows marked diffuse changes in the anterior lobe of the pituitary. There is extensive infiltration consisting chiefly of lymphocytes, but also plasma cells and, on occasion, eosinophils. Lymphoid follicles with germinal centers are often seen. The reticulin framework of the acini is usually intact, with occasional areas of focal disruption and collapse. The involved gland shows various degrees of destruction, but foci of uninvolved pituitary tissue are morphologically normal. The distinctive absence of granulomata distinguishes this condition from the granulomatous hypophysitis seen in association with tuberculosis, syphilis, sarcoidosis, and giant cell granuloma. Neurohypophysial tissue previously thought to be uninvolved can be infiltrated with inflammatory cells, but this is much less common.

Immunohistochemically, the presence of immunoreactive PRL, GH, ACTH, FSH, LH, and TSH within surviving adenohypophysial cells can be demonstrated. The number of immunopositive cells for each hormone varies depending upon the degree of gland destruction. In cases of autoimmune hypophysitis associated with pregnancy or occurring in the postpartum period, the immunoperoxidase staining reveals pituitary-cell cords enveloped by inflammatory infiltrate containing predominantly PRL cells. The inflammatory cells are a polyclonal population of T and B cells with positivity for leukocyte common antigen (LCA), L-26, UCHL, κ and λ light chains, and D53.

Electron microscopic features reveal adenohypophysial cells infiltrated by various inflammatory cells, including plasma cells, lymphocytes, macrophages, and less commonly eosinophils and neutrophils (Fig. 4). In the areas of most dense inflammatory cell infiltration, pituitary cells show interdigititation, with activated lymphocytes at the common interface. Some of these pituitary cells show oncotypic transformation. In general, the morphologic features of hypophysitis resemble those of other autoimmune endocrinopathies.

- Pathogenetic Mechanisms

The pathogenesis of lymphocytic hypophysitis has been suspected to be autoimmune in origin from the time of its original description (Goudie and Pinkerton 1962). Indeed, several lines of evidence support this hypothesis. Circulating antipituitary antibodies have been detected in a minority of patients with the disease (Ozawa and Shishiba 1993, Thodou et al. 1995). The association of lymphocytic hypophysitis with pregnancy has been explained by the documentation of antibodies that react with nonhormonal antigens in hyperplastic lactotrophs (Bottazzo et al. 1975). Anti-
pituitary antibodies have also been detected in patients with the "empty sella syndrome" (Komatsu et al. 1988), idiopathic GH deficiency (Crock et al. 1993), Cushing's syndrome (Scherbaum et al. 1987), and different autoimmune isolated and polyendocrinopathies without hypophysitis (Bottazzo et al. 1975). In an isolated case of ACTH deficiency, the presence of antibodies to corticotroph antigens was detected in secretory granules that contained neither ACTH nor other POMC-derived peptide (Sauter et al. 1990). Thus, the antigen in question could well be a cell-specific factor required for POMC processing. The different methods for detection and quantification of circulating antipituitary antibodies used in different studies do not permit firm conclusions (Crock et al. 1993, Pouplard 1982). Thus, the exact role of these autoantibodies in the pathogenesis of lymphocytic hypophysitis remains largely unknown.

Specific subtypes of the major histocompatibility complex (MHC) human leukocyte antigens (HLA) can be correlated with a number of autoimmune endocrine disorders. Most HLA antigens have been detected in patients with lymphocytic hypophysitis by some investigators (Asa et al. 1981, Guay et al. 1987, Pestell et al. 1990, Supier and Mickle 1992, Feigenbaum et al. 1991, Meichner et al. 1987, Miyamoto et al. 1988, Pholsena et al. 1994). Others, using immunohistochemistry, did not identify MHC class II positive antigens on pituitary cells from patients with lymphocytic hypophysitis (McCutcheon and Oldfield 1991). It is likely that HLA-DR genes are not responsible for the genesis of the autoimmune response per se but may be closely related, in some subjects, with the genes directly responsible.

Experimentally, subcutaneous injections of human anterior pituitary lobe homogenates in Freund's adjuvant produce a disease histologically similar to lymphocytic hypophysitis characterized by focal lymphoid aggregates and diffuse mononuclear cell infiltration of the pituitary. Interestingly, this adenohypophysitis was found to be more pronounced in pregnant and lactating rats (Levine 1967). Similar results have been obtained by immunization of rabbits with homologous pituitary tissue in complete Freund's adjuvant (Klein et al. 1982). Although induction of hypophysitis in hamsters is associated with the development of antipituitary antibodies, passive transfer of these antibodies does not propagate the disease (Yoon et al. 1992).

- Implications for Management

Management of patients with suspected lymphocytic hypophysitis must be evaluated against the background of the natural history of this condition. Progressive severe and permanent hypopituitarism reflective of the degree of destruction of pituitary cells has resulted in a fatal outcome in almost 20 subjects (Thodou et al. 1995). In contrast, spontaneous recovery of pituitary function with near resolution of the pituitary mass has been described in several cases with histologically proven hypophysitis (Bitton et al. 1991, Ozawa and Shishiba 1993, McGrail et al. 1987, Ober and Elster 1994). In some of these cases, the hypopituitarism may have been due to hypophysial edema rather than to cell necrosis. The majority of patients, however, require active treatment. Although the administration of bromocriptine can improve visual field deficits and lower the hyperprolactinemia, the beneficial impact of this agent on the course of the disease is unproven. Glucocorticoid therapy has been advocated to reduce

Figure 5. Ultrastructural features of lymphocytic hypophysitis. Lymphocytes and plasma cells (arrowheads) invade and disrupt adenohypophyseal parenchyma. Magnification ≈5700.
inflammation and has been temporally effective in some patients (Bitton et al. 1991, Nussbaum et al. 1991, Stelmach and O'Day 1991). The true efficacy of corticosteroids in this condition, however, also remains uncertain. Transphenoidal surgery should be performed in cases associated with progressive compressive features or those in whom radiographic and/or neurologic progression occurs during conservative medical management (Prasad et al. 1991, Nishihoka et al. 1994). Additionally, transphenoidal surgery is both diagnostic and therapeutic. Amelioration of symptoms due to sellar mass effects is usually rapid (Nishihoka et al. 1994, Prasad et al. 1991, Thodou et al. 1995). Similarly, the hyperprolactinemia (Levine et al. 1988, Mazzone et al. 1983, Nussbaum et al. 1991) and pituitary insufficiency (McGrail et al. 1987, Bitton et al. 1991) resolve following pituitary surgery in most cases. In two of our cases, gradual and total recovery of pituitary dysfunction was documented following transphenoidal biopsy (Thodou et al. 1995). In rare instances, surgical intervention has been associated with further deterioration of the visual field deficit (Pestell et al. 1990) and/or the associated hypopituitarism (Stelmach and O'Day 1991, Pestell et al. 1990, Levine et al. 1988, Reusch et al. 1992). These latter complications highlight the importance of early suspicion of the diagnosis and conservative management in patients with nonprogressive disease. In the event that surgery is contemplated, we propose that in cases of suspected hyphophysitis a frozen section should be obtained to confirm the diagnosis to avoid aggressive resection of potentially viable pituitary tissue.

In conclusion, lymphocytic hyphophysitis should be considered in the differential diagnosis of pituitary masses in women, especially during the latter half of pregnancy and in the first 6 months postpartum, as well as in those patients in whom pituitary hormone deficiency is noted in association with a coexisting autoimmune disorder. Other patients who should be suspected of harboring such lesions include those who present with a rapidly enlarging pituitary mass, those whose PRL levels decline marginally, or those who show modest therapeutic responses to bromocriptine. Owing to the lack of specificity of any of the other markers of the disease, the diagnosis can only be currently confirmed with histologic examination. Nevertheless, because of the potentially transient endocrine and compressive features of this condition in many instances, conservative management on the basis of clinical suspicion may eliminate the need for aggressive pituitary surgery.

References


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