Lymphocytic Adenohypophysitis

Michael W. McDermott, Donald E. Griesdale, Kenneth Berry and G. Edward Wilkins

ABSTRACT: Lymphocytic adenohypophysitis (LAH) is an uncommon disorder in the spectrum of pituitary disease. Twenty-three cases proven by biopsy or at autopsy have been reported since 1962. We report 2 further cases and review the etiology, immunology and pathology of the disease. The diagnosis should be considered in a female patient who presents during the post-partum period with the clinical picture of a non-functional or prolactin cell pituitary adenoma and evidence of hypopituitarism.

RÉSUMÉ: Adénohypophysite lymphocytaire. Parmi les maladies de la glande pituitaire, l'adénohypophysite lymphocytaire est une affection très rare. Vingt-trois cas confirmés par biopsie ou à l'autopsie ont été rapportés depuis 1962. Nous rapportons 2 nouveaux cas et nous revoyons l'étiologie, l'immunologie et la pathologie de cette maladie. Ce diagnostic devrait être envisagé chez toute femme qui présente, en post-partum, un tableau clinique d'adénome pituitaire non fonctionnel ou à prolactine et des signes d'hypopituitarisme.


Lymphocytic adenohypophysitis (LAH) is an uncommon pituitary disorder. It occurs exclusively in women, often during the post partum period and can mimic a non-functional or prolactin cell pituitary adenoma. It is generally agreed that lymphocytic adenohypophysitis is an autoimmune disease. More recently, it has been suggested that it may be part of a polyglanular autoimmune syndrome. There is evidence to support a role for both cell-mediated and humoral autoimmune destruction of the gland.

Since 1962, 23 cases of LAH have been reported in the literature. Each, the diagnosis has been made by biopsy or at autopsy. The patients present with symptoms of headache, malaise, weakness and other symptoms of endocrine dysfunction. Compression of the optic chiasm has been documented in six cases. Approximately 70% of these patients have had the onset of symptoms between the second trimester and the tenth month post-partum. The rate at which hypopituitarism develops is often more rapid than in those patients with pituitary adenoma. Several cases of selective hormonal loss have been reported. In all cases the anterior pituitary is infiltrated by lymphocytes and plasma cells with destruction of normal gland. Ase et al have documented the pathology with electron microscopy and characterized the condition as a distinct clinicopathologic entity. We report two further cases of LAH and review the etiology, immunology, and pathology of the disease.

CASE REPORTS

Case 1
A 31-year-old woman, gravida 5, para 4, developed retro-orbital headaches and blurred vision during the third trimester of pregnancy. There was no past history of pregnancy-induced hypertension. Physical examination was normal for gestational dates except for a bitemporal superior quadrantanopia, confirmed by Goldman visual fields. Visual acuity was normal. Skull x-rays were normal. Laboratory investigations revealed: serum prolactin 80 ng/mL (normal less than 4000 ng/mL), free thyroxine 11 pmol/L (normal = 10 - 36 pmol/L), TSH < 2.0 mU/L (normal = 0.5 - 4.0 mU/L), cortisol am/pm 595 nmol/L - 433 nmol/L (normal = 110 - 520 pmol/L), growth hormone 1.2 mg/L (normal = 0 - 5 mg/L), LH 22 IU/L (normal = 0 - 20 IU/L), FSH = 11 IU/L (normal = 8 - 40 IU/L).
Because of a concern regarding the possibility of a pituitary tumour the patient was admitted to hospital and labour induced at 39 weeks gestation. Delivery was uncomplicated but two days post-partum the patient complained of worsening vision. CT scan demonstrated an enhancing cystic lesion of the pituitary with suprasellar extension (Figure 1). Bromocriptine 2.5 mg twice daily was started with some improvement in visual fields but discontinued due to nausea and vomiting after two days.

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Transsphenoidal exploration revealed a firm, pale mass within the gland. No cyst was encountered and there was little bleeding. A limited decompression was carried out. The normal gland appeared displaced posteriorly. Post-operatively, transient diabetes insipidus developed.

Pathologic examination of the pituitary tissue showed massive infiltration of the anterior lobe by lymphocytes and plasma cells with destruction of parenchymal cells, and fibrosis (Figure 2). Immunohistochemical staining revealed growth hormone and prolactin in a few surviving adenohypophysial cells.

Pituitary function testing one month following surgery was compatible with panhypopituitarism. The patient was placed on full hormonal replacement therapy and remains well at 3.5 years follow-up.

Case 2
A 45-year-old woman, gravida 1, para 1, had gradual onset of headaches, fatigue and decreased libido over 1½ months. Two months later there was abrupt cessation of menses and development of polyuria/polydipsia.

Physical examination was normal. Goldman visual fields revealed bitemporal superior quadrant defects, greater on the left. Visual acuity was normal. Laboratory tests revealed serum prolactin 21 mg/L (normal = 0-20 mg/L), serum thyroxin 59 nmol/L (normal = 51-142 nmol/L), TSH < 2.0 μU/L, cortisol <1 pmol/L, with no response to hypoglycemia, growth hormone less than 1.2 ppmg/L with no response to hypoglycemia, LH/FSH less than 2 IU/L, with no response to gonadotropin releasing hormone. A water deprivation test confirmed central diabetes insipidus.

Skull x-rays were normal. A CT scan revealed a homogeneously enhancing lesion with suprasellar extension (Figure 3). At transsphenoidal operation, fibrous tissue was found. There was no obvious necrotic tissue and the mass was relatively avascular. Histologic examination revealed a diffuse lymphocytic infiltrate and destruction of normal gland (Figure 4). Immunohistochemical staining results were unavailable.

Post-operatively the patient required ongoing hormonal replacement with cortisone acetate, l-thyroxine and DDAVP. She remains well at two years follow-up.

**Discussion**

Lymphocytic adenohypophysitis is an uncommon disorder of the pituitary gland first described by Goudie and Pinkerton in 1962. They reported a 22-year-old woman who developed symptoms of hypopituitarism after the birth of her second child.
Table 1: Biopsy or autopsy proven cases of lymphocytic adenohypophysitis 2-3, 16-32

<table>
<thead>
<tr>
<th>Author</th>
<th>Age Onset of Symptoms (Post-Partum)</th>
<th>Hypopituitarism</th>
<th>Other Autoimmune Disease</th>
<th>Visual Field Defect</th>
<th>Elevated Prolactin</th>
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<tbody>
<tr>
<td><strong>Group 1 — Onset related to Pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Goude (1962)</td>
<td>22 (2 mo.)</td>
<td>Yes</td>
<td>Thyroiditis</td>
<td>No</td>
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<tr>
<td>Egloff (1969)</td>
<td>29 (4 wks.)</td>
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<td>No</td>
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<tr>
<td>Quencer (1980)</td>
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<td>No</td>
<td>No</td>
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<td>Yes</td>
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<tr>
<td>Richtsmeier (1980)</td>
<td>31 (3 mo.)</td>
<td>No*</td>
<td>Thyroiditis</td>
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<td>N/A</td>
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<tr>
<td>Mayfield (1980)</td>
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<td>Yes</td>
<td>Adrenalinits</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Asa (1981)</td>
<td>28 (2nd trimester)</td>
<td>Yes</td>
<td>(diabetes insipidus)</td>
<td>No</td>
<td>No**</td>
</tr>
<tr>
<td></td>
<td>29 (3rd trimester)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Portocarrerro (1981)</td>
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<td>Baskin (1982)</td>
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<td>(diabetes insipidus)</td>
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<td>No**</td>
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<tr>
<td>Hungerford (1982)</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>Mazzone (1983)</td>
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<td>Pernicious anemia</td>
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<tr>
<td>Sobrinho-Simoes</td>
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<tr>
<td>Jensen (1986)</td>
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<td>Kurisaka (1986)</td>
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<tr>
<td>Meichner (1987)</td>
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<td>(diabetes insipidus)</td>
<td>No</td>
<td>Yes**</td>
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<tr>
<td><strong>Group 2 — Not Related to Pregnancy</strong></td>
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<tr>
<td>Hume (1967)</td>
<td>74</td>
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<td>Thyroiditis atrophic gastritis</td>
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<td>Lack (1975)</td>
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</tr>
<tr>
<td>Cebelin (1981)</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No +</td>
</tr>
<tr>
<td>Madson (1985)</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Wild (1986)</td>
<td>31</td>
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<td>No</td>
<td>No</td>
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* = clinical signs of hypocorticilism  
** = suprasellar extension on CT scan  
+ = within 12 months post-partum  
N/A = not available  

and suffered peripheral circulatory collapse following removal of a gangrenous appendix. Post mortem examination revealed a lymphocytic infiltrate of the pars anterior and pars intermedia and changes of the thyroid gland consistent with Hashimoto's thyroiditis. They concluded that the occurrence of the two diseases was not coincidental and postulated an autoimmune reaction to the release of pituitary and thyroid antigens during post partum involution of these glands. Since then, an additional 22 cases have been described (Table 1). All are women, ages 22 to 74, and in 16 of 23 the onset of symptoms has occurred between the second trimester and the tenth month post-partum. Seven have had evidence of concurrent autoimmune disease. In contrast to pituitary adenomas the onset of hypopituitarism has been more rapid and has been supported by history and/or laboratory tests in 14. Serum prolactin levels were evaluated in 6 of 14 patients tested and of these 3 had some degree of hypopituitarism. Optic chiasm compression was present in 6 of 23 patients. CT scans were performed in 11 patients and in 7 there was evidence of suprasellar extension. In one of our patients (Case 1) the onset was related to pregnancy. Neither patient had evidence of other autoimmune disease and both developed hypopituitarism. Although clear evidence of hormonal insufficiency developed one month post...
operatively in Case 1 this was not felt to be related to the surgical procedure per se, as only a limited biopsy and decompression was carried out. Both patients had resolution of visual field defects post-operatively. One of our patients had persisting diabetes insipidus and this has been reported in four patients previously. 2, 3, 15, 16

The incidence of LAH is not known. In a series of 100 unselected consecutive autopsy specimens Shanklin found lymphocytic infiltrates in 43 of 100 specimens. The pars intermedia was the most frequent site for lymphocytic infiltration and there was no case in which the pars anterior was involved. 13 Other cases of hypopituitarism suspected to be related to autoimmune phenomena have been reported although histologic confirmation is lacking. 8, 34-38 Often in these patients there is concurrent autoimmune disease and frequently the hormone loss is selective.

The etiology of the disorder is unclear with evidence to support both cell mediated and humoral autoimmune mechanisms. Triplett was able to demonstrate that autoimmune destruction of the pituitary did occur. 39 In his experiment, hypophysectomized free frog embryos rejected their own re-implanted pituitaries in adult life, indicating that the sequestered pituitary antigens were regarded as "foreign" by the competent immune system. Levine developed a reproducible model of LAH supporting cell mediated mechanisms. 40 He injected pituitary extract and Freud's adjuvant into the footpad of mice and demonstrated lymphocytic infiltration of the pituitary. Klein et al showed a correlation between pituitary histologic changes and lymphocyte blast transformation in a rabbit model of LAH. 13 This data, along with absence of antipituitary antibodies in experimental animals and controls, was thought to give further support to cell mediated mechanisms in the pathogenesis of the disease.

Engelberth and Jezkova 41 were the first to associate antipituitary antibodies with the development of hypopituitarism in post partum women. They found that 18% of women with Sheehan's syndrome had anti-pituitary antibodies 5-7 days post partum. At 6-12 months, 25% of those with antibodies had signs of hypopituitarism compared to only 4% of those without antibodies. Botazzo et al found anti-prolactin cell antibodies in 19 of 287 patients with other autoimmune diseases. 11 Although no pituitary antibodies were found in patients with panhypopituitarism, it was suggested that cases of isolated hormone deficiency could be explained by the absence of specific antibodies. Subsequently, isolated growth hormone deficiency in a girl with Turner's syndrome and antigrowth hormone antibody, and antibodies to LH/FSH secreting cells in children with cryptorchidism have been reported. 10, 37

Recently Jensen et al 42 reported a patient with isolated corticotropin deficiency and post partum LAH. They demonstrated B cells, Leu 2a + (suppressor and cytotoxic) Leu 3a + (helper/inducer) T cells, macrophages and plasma cells infiltrating the gland. Anti-corticotroph cell antibodies could not be found and they felt this picture was not conclusive in implicating either cellular or humoral immunity in the development of the disease.

It has been suggested that LAH may be part of the polyglandular autoimmune disorders. 8, 38 In 1972 Arvanitakis et al reported the occurrence of selective hypopituitarism in two patients with chronic cutaneous candidiasis, which is often associated with other endocrinopathies and impaired cell mediated immunity. 40 Seven patients with LAH from the literature have had evidence of autoimmune disease involving other organs. 2, 3, 21, 24, 27, 30, 31 Barkan et al recently reported two men with polyglandular autoimmune syndromes and isolated gonadotropin deficiency after puberty. 4 They failed to respond to bolus and pulsed doses of gonadotropin releasing hormone, while secretion of other anterior pituitary hormones was unaffected. Although pituitary antibodies were not found and pituitary biopsy was not done, the authors suggested that autoimmune hypophysitis may be part of a polyglandular autoimmune syndrome and that hormone loss could be selective.

Viral infection may have a role in the production of multiple-organ antibodies, LAH and polyendocrine disease. Haspel et al showed that when spleen cells from mice infected with reovirus type I were fused into myeloma cells, the hybridomas produced antibodies to islet cells, gastric mucosal cells and cells of the anterior pituitary. 43 Insulin dependent diabetes, a disease linked with previous viral infection and autoimmune destruction of islet cells, has been associated with the production of autoantibodies to multiple organs. 44, 45 Sotah et al were able to raise human mononuclear antibodies from insulin dependent diabetics and 36.6% of their relatives with islet cell antibodies in their sera had antibodies to pituitary cells. 46 This data supports a role for virus-induced autoimmune mechanisms in the development of polyendocrine disease and possibly LAH.

The onset of LAH associated with pregnancy, as observed by Goudie and Pinkerton, is not coincidental. 47 Levine noted more severe disease in pregnant mice in his experimental model of LAH. 48 Engelberth and Jezkova 41 found that 18% of women with Sheehan's syndrome had anti-pituitary antibodies 5-7 days post partum and that 25% went on to develop signs of hypopituitarism. Whether pregnancy is associated more often with disease because of increased exposure to pituitary antigens with increasing pituitary size and blood flow, or because of alteration in maternal immunologic status is not known. The exposure during pregnancy to fetal antigens and antibody may lead to cross reaction with maternal antigens. 16 Loss of fetal suppressor substances in the post partum period may be responsible for cross reactivity of the autoantigens and new, or worsening of pre-existing, autoimmune disease. 43, 46

Portaciorro et al 49 have suggested several possible mechanisms for the elevated prolactin levels seen in cases of LAH not related to pregnancy: 1) distortion of the portal system with increased size of the gland and reduced delivery of dopamine; 2) mediators of inflammation stimulating prolactin secretion or blocking dopamine receptors and; 3) presence of a prolactin stimulating antibody. It is most likely that with supra-sellar extension, the infundibulum is compressed by the inflamed gland. The improvement in vision noted on one of our patients and another previously reported with bromocryptine treatment would support either of the first two mechanisms.

The pathology of LAH has been described by Assa and others. 15 Typically the gland shows a diffuse lymphocytic and plasma cell infiltrate, occasional lymphoid follicles with germinal centers, and destruction of adenohypophysial cells. There are no epithelial cells or granuloma formation. In areas of cell injury, immunohistochemical staining for functional adenohypophysial cells yields negative results. The differential diagnosis by light microscopy includes sarcoidosis, syphilis, TB, granulomatous hypophysitis and post partum hemorrhagic infarction. 44 Electron microscopic features include interdigititation by lymphocytes
and adenohypophysial cells, fusion of lysosomes with secretory granules and swollen mitochondria indicating oncocytic transformation. In the two reported cases studies by electron microscopy there was no evidence of immune complex deposits or vascular injury.\textsuperscript{15}

CONCLUSIONS

Lymphocytic adenohypophysitis in an uncommon disorder which occurs most often in women and in 70% of the cases the onset is temporarily related to pregnancy. These patients have a rapid onset of hypopituitarism as distinct from patients with non-functional or prolactin cell adenomas.

At present the disease is thought to be of autoimmune origin and may be part of the polyglandular autoimmune syndromes. Whether humoral or cellular immunity is primarily involved in the pathogenesis remains unresolved. Until better serologic or cellular markers of the disease are available, pituitary biopsy is necessary for diagnosis and for relief of optic pathway compression.

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REFERENCES
