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Autoimmune Hypophysitis

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Autoimmune (lymphocytic) hypophysitis is a rare disease that should be considered in the differential diagnosis of any nonsecreting pituitary mass, especially when occurring during pregnancy or postpartum. We have analyzed 370 articles published from January 1962 to October 2004 and identified a total of 379 patients with primary lymphocytic hypophysitis. The present review synthesizes the clinical and research data reported in this body of scientific literature. (*Endocrine Reviews* 26: 599–614, 2005)

I. Introduction: Definition and Classification

AUTOIMMUNE HYPOPHYSITIS (AH), often referred to as lymphocytic hypophysitis, is the most common among the chronic inflammations that primarily affect the pituitary gland, surpassing granulomatous and xanthomatous hypophysitides (Table 1). It was originally labeled lymphocytic adenohypophysitis (LAH) because the inflammation was thought to be limited to the anterior hypophysis. When it was later realized that the autoimmune infiltrate could involve the infundibular stem and the posterior lobe exclusively, the term lymphocytic infundibuloneurohypophysitis (LINH) was created. Finally, it was recognized that both the adenohypophysis and the infundibuloneurohypophysis could be affected; hence, the term lymphocytic panhypophysitis (LPH). Upon review of the literature, we identified 379 patients with primary lymphocytic hypophysitis and classified them morphologically into LAH, LINH, and LPH (Table 2). It is unknown at this time whether these entities represent different diseases or different aspects of the same disease. The classification was based on pituitary histology, when available, or on imaging and endocrine studies alone when surgery was not performed. It is important to emphasize that, even when based on histology, the classification may be inaccurate because of sampling problems. For example, a pathological process that involves both the anterior and the posterior pituitary lobe may be diagnosed as LAH if the surgical specimens were small or obtained only from the anterior lobe.

Granulomatous hypophysitis was first described in 1917 by Simmonds (1) who examined 2000 pituitaries at autopsy and found four cases not related to tuberculosis or syphilis. The first antemortem case was reported in 1980 (2). The disease is rare, affects males and females in equal proportions, and presents with nausea, vomiting, diabetes insipidus, and hyperprolactinemia. The pituitary shows diffuse collections of multinucleated giant cells and histiocytes, with surrounding lymphocytes and plasma cells. Lymphocytes are mainly of the T lineage (3); giant cells often display anisotropic, prolactin (PRL)-containing, cytoplasmic inclusions (4). Granulomatous hypophysitis can occur together with lymphocytic hypophysitis (5–7). For this reason McKeel (8) suggested that the two diseases represent an autoimmune spectrum from a purely lymphocytic form constituting the predominant early lesion to a granulomatous form appearing later. Granulomatous hypophysitis, however, appears distinct from lymphocytic hypophysitis because it lacks key epidemiological features that are present in lymphocytic hypophysitis, such as female bias, association with pregnancy, occasional spontaneous resolution, and association with other well-established autoimmune diseases.

Xanthomatous hypophysitis was originally described in three women in 1998 (9) and in six other patients thereafter (10–13). The pituitary shows cystic-like areas of liquefaction, infiltrated by lipid-rich foamy histiocytes and lymphocytes. These lesions resemble those described in extrapituitary sites, such as gallbladder, endometrium, middle ear, mastoid, and choroid plexus (14). Given the cystic nature of these

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Abbreviations: ADH, Antidiuretic hormone (vasopressin); AH, autoimmune hypophysitis; LAH, lymphocytic adenohypophysitis; LINH, lymphocytic infundibuloneurohypophysitis; LPH, lymphocytic panhypophysitis; MHC, major histocompatibility complex; MRI, magnetic resonance imaging; PRL, prolactin.

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TABLE 1. Pathological classification of the main forms of hypophysitis

Primary forms
Lymphocytic (autoimmune)
Granulomatous
Xanthomatous
Secondary forms
Local lesions
Germinomas
Rathke's cleft cysts
Craniopharyngiomas
Pituitary adenomas
Systemic diseases
Sarcoidosis
Wegner's granulomatosis
Langerhans cell hisitocytosis
Syphilis
Tuberculosis

lesions, some authors consider xanthomatous hypophysitis an inflammatory response to components of ruptured cysts. The rarity of this disease, however, has hampered understanding of its pathogenesis, natural history, and prognosis. Similar limitations apply to necrotizing hypophysitis, which has been demonstrated histologically only in two patients (15) and suspected radiologically in a third (16). Histologically, the pituitary appears to be destroyed by diffuse necrosis with surrounding lymphocytes, plasma cells, and a few eosinophils. It is unknown whether necrotizing hypophysitis represents a separate disease or a variant of the other three main histological types.

The term "secondary hypophysitis" was introduced by Puchner and colleagues (17) to indicate a pituitary inflammation that originates from neighboring lesions or is part of systemic diseases (Table 1). In secondary hypophysitis the infiltrate is mainly lymphocytic or xanthogranulomatous and focuses around the lesion rather than diffusing to the entire gland. Among the systemic diseases that can involve the pituitary, sarcoidosis (18), Wegner's granulomatosis (19), and Langerhans cell histiocytosis (20) are now the most common. We identified 14 patients with lymphocytic hypophysitis secondary to neighboring lesions, represented by five germinomas (21–24), four Rathke's cleft cysts (25–28), three craniopharyngiomas (29), and two GH adenomas (30, 31). Lymphocytic infiltrates can also be seen in about 3% of pituitary adenomas but are typically small, perivascular, and almost exclusively composed of T cells (32).

Uncertainty still exists about the appearance of the normal pituitary at autopsy and, in particular, on whether it normally harbors a few lymphocytes. Simmonds and Brandes (33) examined 200 pituitaries in serial sections from patients who had died suddenly; thus, no clinical correlation was available. They found 21 cases (10%) showing areas of lymphocytic infiltration. Seventeen of the infiltrates were present in the pars intermedia, two in the posterior lobe, and two in the anterior lobe. Zanchi and Dova (34) analyzed 150 pituitaries from unselected individuals who had died from usual causes, and found 70 cases (47%) with a pure lymphocytic infiltrate in the pars intermedia. Their finding was confirmed by Shanklin (35), who examined 100 pituitaries at autopsy and found 43 cases (43%) of lymphocytic infiltration within or near the pars intermedia. Finally, Scheithauer *et al.* (36) studied 69 pituitaries at autopsy from women who had died during pregnancy, after abortion, or in the postpartum period. Five pituitaries (7%) showed focal lymphocytic infiltration, although the exact anatomic location was not mentioned. Despite the paucity of data and the lack of clinical correlation, it seems reasonable to conclude that lymphocytes in or near the pars intermedia are a normal finding (perhaps an embryological vestige of the pharyngeal adenoid tissue). In contrast, lymphocytes within the anterior or posterior lobe should be considered pathological.

II. Historical Notes

LAH was first described in 1962 by Goudie and Pinkerton (37). They reported a 22-yr-old woman who died 14 months after her second delivery, probably because of adrenal insufficiency. Twelve months postpartum she felt increasingly tired and noticed enlargement of her neck. She was admitted to the hospital for vomiting, diarrhea, and severe lower abdominal pain radiating to the right iliac fossa, and thus was brought to the operating room for suspected appendicitis. Surgery revealed an acutely inflamed, gangrenous appendix that had not ruptured. The appendix was removed, but 8 h later the patient developed circulatory shock and died. The autopsy showed a firm, enlarged thyroid gland infiltrated with lymphocytes, atrophic adrenal glands, and a small pi-

TABLE 2. Classification of 379 patients with primary lymphocytic hypophysitis based on the anatomical location

	No. of patients
LAH (n = 245)	
Histology shows infiltrated A and normal N.	25
Histology shows infiltrated A. N was not recorded, but no symptoms of DI.	157
Clinic and imaging show A involvement, but no symptoms or radiological signs of DI.	51
Clinic shows A involvement, but not DI. Imaging was normal or not done.	12
LINH (n = 39)	
Histology shows infiltrated N and normal A.	5
Histology shows infiltrated N. A was not recorded, but no symptoms of A involvement.	21
Clinics and imaging show N involvement, but no symptoms or signs of A involvement.	13
LPH (n = 95)	
Histology shows infiltrated A and infiltrated N.	25
Histology shows infiltrated A. N was not recorded but symptoms or radiological signs of DI.	32
Histology shows infiltrated N. A was not recorded but symptoms of A involvement.	3
Clinics and imaging show A involvement and DI.	35

A, Anterior hypophysis; N, infundibuloneurohypophysis; DI, diabetes insipidus.

tuitary. The adenohypophysis was extensively infiltrated by lymphocytes and few plasma cells, aggregating in some areas to form lymphoid follicles. The neurohypophysis was normal. Noting the presence of Hashimoto's thyroiditis, a well-characterized autoimmune disease, the authors concluded that the coexistence of lymphocytic thyroiditis and mononuclear cells infiltration of the anterior pituitary was not fortuitous. They speculated that both diseases could be explained by the "onset of autoimmune reaction to thyroid and pituitary antigens released during the puerperal involution of these glands." Goudie and Pinkerton were apparently the first to postulate the autoimmune nature of this condition, at a time when the modern field of autoimmunity research had just begun. Earlier cases are probably hidden in hospital archives or published without recognition of the disease (38, 39). The first antemortem diagnoses of LAH, established on transphenoidal biopsy, were reported in 1980 almost simultaneously by Quencer (40) and Mayfield *et al.* (41).

LINH was first described in 1970 by Saito *et al.* (42) who observed a 66-yr-old asthmatic woman with 1-month history of severe dehydration that responded strikingly to the administration of pitressin. Two months after discharge, however, she developed a severe attack of bronchial asthma and died. Autopsy revealed marked infiltration of neurohypophysis and infundibular stem with lymphocytes and plasma cells, aggregating in some areas in lymphoid follicles. The adenohypophysis was normal except for vacuolar degeneration of the basophilic cells, likely due to the prolonged use of glucocorticoids for asthma. A second patient was reported in 1989 at autopsy (43), and a third patient was reported in 1991 based on clinical and imaging findings (44).

LPH was first described in 1991 in a 40-yr-old male with a 3-month history of headache, impotence, polyuria, and polydipsia (45). Transphenoidal surgery found a sella turcica filled with whitish, fibrous tissue. Histology revealed extensive infiltration of adenohypophysis and neurohypophysis by lymphocytes, plasma cells, and histiocytes.

III. Data Sources and Methods of Analysis

This review is based on 370 articles published on AH from 1962–2004, mainly case reports or small case series. The articles were identified as follows: 1) PubMed searches using the keywords *hypophysitis*, *adenohypophysitis*, *infundibul**, *lympho** and *hypophys**, *autoimmu** and *hypophys**, *lympho** and *adenohypophys**, *autoimmu** and *pituit**; 2) citations in the papers identified in PubMed; and 3) citations in numerous textbook chapters. The articles were in English (n = 295), Japanese (n = 42), French (n = 13), Spanish (n = 6), Korean (n = 5), German (n = 4), Italian (n = 2), Chinese (n = 1), Dutch (n = 1), and Slovak (n = 1), and described a total of 379 patients with primary lymphocytic hypophysitis (Table 2). The complete bibliography can be viewed and downloaded from the Johns Hopkins Hypophysitis Research Center web site (46). The present review extends the eight reviews previously published on AH (47–54) and synthesizes all the available clinical and scientific findings.

We have also abstracted the clinical information from this aggregate case series of 379 patients and entered it in a database that can be freely downloaded from the Johns Hopkins Hypophysitis Research Center web site (46). Table 3 lists the key variables included in this database. All analyses were performed using Stata statistical software, release 8 (Stata Corp., College Station, TX).

IV. Epidemiology

AH has been described in 27 of the 193 sovereign nations of the world, but principally in Japan (130 of the 379 cases, 34%), United States (82 cases, 22%), United Kingdom (28 cases, 7%), Germany (27 cases, 7%), and Canada (19 cases, 5%). It is unknown, however, whether this reflects any true geographic or ethnic variation in risk or, as is more likely, whether this means only that diagnosis of the condition varies. Insufficient population-based data exist to estimate the incidence of AH, although, undoubtedly, it is a rare condition. Clinical series of unselected surgical specimens can be useful in establishing preliminary estimates of disease incidence, because other conditions requiring pituitary surgery are etiologically distinct from AH. Buxton and Robertson (55) analyzed 619 consecutive pituitary surgeries performed over 15 yr at Nottingham, UK, and found five cases of AH (0.8%). Considering that their hospital was the sole provider of surgery for pituitary masses in this community of approximately 3 million, the annual incidence of AH can be estimated at one case per 9 million. Data from three other clinical series, where population denominator estimates are unavailable, corroborate the finding that AH is seen in less than 1% of all surgical pituitary specimens. Sautner *et al.* (17) and Fehn *et al.* (56) analyzed 2500 surgical pituitary specimens collected at Hamburg, Germany, from 1970–1996 and found six cases (0.24%). Honegger *et al.* (57) analyzed 2362 specimens collected from 1982–1995 in Erlagen, Germany, and found seven cases (0.30%). Recently, Leung *et al.* (58) reported 13 cases among 2000 patients who underwent transphenoidal surgery for pituitary mass lesions in Charlottesville, VA, from 1992–2003 (0.65%). We reviewed the Johns Hopkins Hospital surgical pathology archives from 1986–2004 and found a similar prevalence value: eight cases in 905 consecutive pituitary specimens (0.88%).

The frequency of case reports of AH has increased with time in the literature. In the first 20 yr since its description

TABLE 3. Key variables included in the database of patients affected by AH

Sex	Anatomic classification
Age	Surgical treatment
Association with pregnancy	Medical treatment
Association with other autoimmune diseases	Other types of treatment
Symptoms at presentation	Details on pathological findings
Endocrinological assessment	Details on mass-reducing treatment
Imaging studies	Details on hormone replacement
Pituitary antibodies	Follow-up time
Method of diagnosis	Status upon follow-up

This database can be downloaded from the Hypophysitis Research Center web site (http://pathology2.jhu.edu/hypophysitis).

(1962–1981), only 16 cases were reported (11 at autopsy and five from surgical pathology specimens). In the next 20 yr (1982–2001), 290 cases were described, and 73 cases have been reported between 2002 and 2004. This greater frequency of reporting is likely related to ascertainment. The recent increase in the use of noninvasive pituitary imaging and transphenoidal surgery likely contributes to increasing the diagnosis of AH, as does the growing general awareness of the condition in the medical community. The 1 per 9 million per year incidence estimate derived from the data of Buxton and Robertson (55) may well be an underestimate of today's incidence, also considering that some AH cases may still go undiagnosed because of their indolent, subclinical course.

LAH is more common in women (210 women and 35 men reported; F:M ratio, 6:1), who tend to present at a younger age (35 ± 13 yr) than males (45 ± 14). In a significant percentage of women LAH manifests during pregnancy or postpartum. LINH appears to affect males and females equally (20 women and 19 men reported). LPH is slightly more common in women (62 women and 33 men reported; F:M ratio, 1.9:1). Both LINH and LPH have a mean age at presentation (42 ± 17 yr) that is significantly higher than that of LAH occurring in women and do not show association with pregnancy.

V. Association between Pregnancy and LAH

LAH shows a striking temporal association with pregnancy (59, 60). Of the total 210 women with LAH, 120 (57%) presented during pregnancy or postpartum. As shown in Fig. 1, where the distribution of symptoms appearance is plotted in relation to delivery (indicated as wk 0), most patients presented in the last month of pregnancy or in the first 2 months after delivery. When occurring in pregnancy, AH does not cause complications on the fetus or on the outcome of pregnancy, which typically concludes at term with spontaneous vaginal delivery. Only one patient died in labor (61). In addition, a history of previous pregnancies does not increase the risk of developing AH in subsequent pregnancies. Similarly, a history of AH does not preclude the patient from having subsequent pregnancies (62–65), considering that 16 women became pregnant after a diagnosis of AH.

This striking temporal association is one of the most interesting features of AH but remains unexplained. The pituitary undergoes a remarkable transformation during pregnancy. Its size increases by about 30% (66), mainly because of the estrogen-driven hypertrophy and hyperplasia of the lactotrophs (67), an increase that may lead to release of pituitary antigens (68). In addition, the massive hyperestrogenemia of pregnancy changes the pattern of pituitary blood flow such that more blood derives from the systemic circulation and less from the hypothalamic-pituitary portal circulation (69). It is thus possible that the pituitary becomes more accessible to the immune system during pregnancy. Pregnancy can also unmask a latent pituitary insufficiency and thus bring more cases to medical attention.

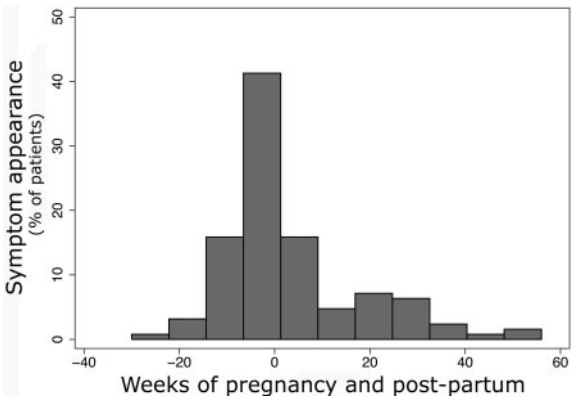

FIG. 1. Distribution of symptom appearance in relation to delivery (indicated as wk 0) in AH. Note the clustering in late pregnancy and early postpartum.

The immune system in the uterine environment changes significantly during pregnancy. Indeed, it is still a mystery why the mother does not reject fetus and placenta, which carry paternal antigens and thus should be analogous to allografts and be subject to the laws of transplantation. This immunological paradox of pregnancy has fascinated generations of scientists. In 1953, Medawar (70) gave three reasons for the lack of fetus rejection: the fetus is antigenically immature; the fetus is anatomically separated from the mother; the maternal immune system is "paralyzed" or "inert" during pregnancy. We now know that pregnant women make antibodies directed against the father's major histocompatibility complex (MHC) antigens, indicating that the fetus is indeed recognized as foreign (71). Also, traffic of cells between mother and fetus occurs during pregnancy, with quantitatively greater transfer in the mother-to-fetus direction (72). Finally, the whole maternal immune system during pregnancy is not suppressed but capable of mounting a response against live infectious agents or vaccines (73). Although the hypotheses of Medawar have been largely abandoned, they stimulated the quest for fresh understanding of how the fetus evades the maternal immune system. Modern studies have focused on the placenta and decidua, which are now known to possess an array of mechanisms effective at suppressing locally the maternal immune system (74–79).

Pregnancy influences the course of autoimmune diseases in different ways. In rheumatoid arthritis (80), Graves' disease (81), and type 1 diabetes mellitus (82, 83) pregnancy typically improves disease course. In scleroderma (84), Sjögren's syndrome (85), and thrombocytopenic purpura (86), there are no significant gestational changes. In systemic lupus erythematosus (87) and myasthenia gravis (88), the effect of pregnancy is unpredictable (either improved, unchanged, or deteriorated). Finally, other autoimmune diseases, such as Wegener's granulomatosis (89, 90), worsen during pregnancy. We do not know, however, of any other autoimmune disease in which pregnancy is so strongly associated with disease onset as in LAH. Identifying the causes underlying this association will promote our understanding of the immune regulation that occurs during pregnancy and may impact our clinical practice.

VI. Clinical Presentations

The clinical presentation of AH is variable and comprises four categories of symptoms: sellar compression, hypopituitarism, diabetes insipidus, and hyperprolactinemia (Table 4).

TABLE 4. Percentages of patients with LAH, LINH, or LPH presenting with the symptoms indicated on the left

Symptom	LAH (%)	LINH (%)	LPH (%)	LAH *vs.* LINH	LAH *vs.* LPH	LINH *vs.* LPH
Headache	53	13	41	0.0001	0.045	0.0023
Visual disturbances	43	3	18	0.0001	0.0001	0.070
Hypocortisolism	42	8	19	0.0001	0.001	0.106
Hypothyroidism	18	0	17	0.005	0.871	0.007
Hypogonadism	12	3	14	0.078	0.669	0.057
Inability to lactate	11	0	5	0.028	0.094	0.146
Polydipsia-polyuria	1	98	83	0.0001	0.0001	0.025
Hyperprolactinemia	23	5	17	0.011	0.227	0.073

The *three columns on the right* report *P* values, which are based on pairwise comparisons using the Wilcoxon rank-sum test.

Symptoms of sellar compression, represented by headache and visual disturbances, are the most common and usually the initial complaint. Headache is considered the result of distension and distortion of the dura mater and diaphragma sellae by the expanding pituitary mass. A recent study of patients with pituitary tumors, however, has shown that pituitary volume does not correlate with severity, duration, and frequency of headache, suggesting that the headache associated with pituitary masses may not be simply a structural problem (91). Visual abnormalities include visual field defects and decreased acuity that are secondary to compression of the optic chiasm by the upwardly expanding pituitary mass. More rarely (14 of 379 patients; 3.7%), patients develop diplopia because of the lateral expansion into the cavernous sinus, with compression of the III, IV or VI cranial nerve and subsequent ocular misalignment (45, 92, 93).

Next most common are symptoms due to a partial or complete deficit of the anterior pituitary hormones, mainly ACTH followed by TSH, gonadotropins, and PRL. These defects are considered the direct result of the autoimmune attack on the pituitary acinar cells. They produce the classic signs and symptoms of hypoadrenalism, hypothyroidism, and hypogonadism. The deficit of PRL manifests itself in the postpartum as inability to lactate.

Next are symptoms due to deficit of the posterior pituitary (diabetes insipidus), which can be attributed either to direct immune destruction or to compression of the posterior lobe and infundibular stem. Considering that diabetes insipidus is rarely seen in pituitary adenomas, we favor the first mechanism. Diabetes insipidus is the cardinal feature of LINH, along with lymphocytic infiltration of the neurohypophysis and radiological findings (94). Diabetes insipidus can also be seen in pure LAH, despite the absence of lymphocytic infiltration in the neuro-infundibulum, because swelling of the pars tuberalis of the adenohypophysis, which covers the infundibulum anterolaterally, may inhibit the axonal transport of antidiuretic hormone (ADH) (95). Diabetes insipidus can be masked in the presence of a coexisting glucocorticoid deficit (96). Glucocorticoids, in fact, oppose the action of ADH at several levels. They inhibit the secretion of ADH from the neurons of the paraventricular nucleus (97), which also synthesize CRH and corelease it with ADH at the median eminence into the portal hypophyseal system (98). In addition, glucocorticoids suppress the synthesis of aquaporin 2, an ADH-dependent water channel expressed in the collecting tubuli of the kidney (99). Thus, in the absence of glucocorticoids, ADH release and aquaporin 2 synthesis are increased, resulting in an antidiuretic effect that masks the increased diuresis due to the ADH deficiency (100, 101).

Least common are the manifestations of hyperprolactinemia, mainly represented by amenorrhea/oligomenorrhea and galactorrhea. Several mechanisms have been invoked to explain this increase in PRL. Stalk compression, with resulting decrease in dopamine delivery to the anterior pituitary, is certainly the best characterized and accounts for the hyperprolactinemia associated with suprasellar masses. The inflammatory process may directly destroy the lactotrophs, inducing release of PRL into the general circulation (similar to the release of preformed thyroid hormones seen in destructive thyroiditides such as type 2 amiodarone-induced thyrotoxicosis and subacute thyroiditis), or may compromise the production of hypothalamic dopamine or the expression of dopaminergic receptors. Finally, the presence of antibodies that stimulate the synthesis and release of PRL, similar to the TSH-stimulatory antibodies seen in Graves' disease, has been proposed (102, 103), although not formally demonstrated. In patients with systemic lupus erythematosus, however, antibodies capable of increasing PRL levels have been reported (104, 105).

It is very unusual for AH to present as incidentaloma (106) (*i.e.*, as a pituitary mass discovered serendipitously by imaging studies in the absence of symptoms or signs suggestive of pituitary disease). Most pituitary incidentalomas, in fact, turn out to be microadenomas (<3 mm) or cysts (107) and typically follow a benign course (108).

As indicated in Table 4, presenting symptoms vary depending on whether AH affects the anterior lobe, the posterior lobe, or both. Visual disturbances, hypocortisolism, and inability to lactate are more common in LAH than in LINH or LPH. In contrast, polydipsia and polyuria suggest LINH, a condition in which other presenting symptoms are rare (visual disturbances, amenorrhea/galactorrhea, and hypogonadism) or not described (hypothyroidism and inability to lactate). The duration of symptoms before clinical presentation is significantly longer in LAH occurring outside of pregnancy (median, 12 months; 25th –75th percentile, 3–25 months) than in LAH associated with pregnancy (4 months; 2–11 months), LINH (3 months; 2–6 months), or LPH (4 months; 2–7 months) (Fig. 2).

VII. Pathology

The defining pathological feature of AH is the infiltration of the pituitary gland with lymphocytes. Histological sections were available in 268 of the total 379 patients: 243 surgical pathology specimens and 25 autopsies. Lymphocytes usually diffused throughout the gland distorting the

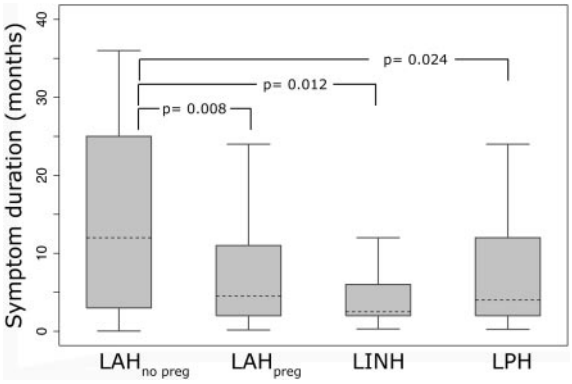

FIG. 2. Duration of symptoms (in months) in patients with LAH not associated with pregnancy ($LAH_{no\ preg}$), LAH associated with pregnancy (LAH_{preg}), lymphocytic infundibulo-neurohypophysitis (LINH), or lymphocytic panhypophysitis (LPH). Each *box* represents the middle 50% of the observations (interquartile range), bordered at the 25th and 75th percentiles, and contains a *dotted line* to indicate the median (50th percentile). The *whisker lines* extend from the *box* to data points that are equal to or less than 1.5 interquartile ranges. Extreme values outside the *whisker lines* are not shown. *P* values are based on pairwise comparisons using the Wilcoxon rank-sum test, performed after the Kruskal-Wallis test ($P = 0.0203$).

normal architecture (Fig. 3A). In 14% of the cases lymphocytes aggregated to form true lymphoid follicles, often with germinal centers. Immunohistochemistry showed a polyclonal mixture of T and B lymphocytes, without a dominant subset, as is typical of autoimmune diseases. In addition to lymphocytes, the immune infiltrate comprises other cells, which likely have a role in the immunopathology (Fig. 3B). Plasma cells were reported in 53% of the cases, eosinophils in 12%, and macrophages, histiocytes, and neutrophils in 6%. Fibrosis was common (47%) and often severe, explaining the whitish discoloration, toughness, and adherence observed by the surgeon upon entering the sella turcica. Pituitary adenomas, in contrast, are usually gray, fleshy, and easy to curette. Necrosis was rare (6%) and usually of modest and focal nature. The above-described pathological features can be identified by the intraoperative analysis of frozen sections, but a definitive diagnosis usually requires the examination of permanent sections.

More recently, mast cells and folliculo-stellate cells have been reported in AH. Mast cells, described by Ehrlich in 1879, have received little attention in the field of autoimmunity until recently, when it was shown that they play a key role in the early phases of autoimmune diseases (109, 110). Mast cells are distributed widely in many organs and tissues, where they typically concentrate around small blood vessels to regulate blood flow and capillary permeability. Vidal *et al.* (111) reported that mast cells are increased in the pituitaries of AH patients, possibly facilitating the homing of autoreactive lymphocytes to the pituitary. Folliculo-stellate cells, described by Farquhar in 1957, surround the endocrine cells of the anterior pituitary with their long cytoplasmic processes. Given their similarity to thymic dendritic cells, folliculo-stellate cells are considered as "professional" antigen-presenting cells (*i.e.*, cells capable of processing and displaying antigens on their surface in the context of MHC class II molecules, and initiating primary T lymphocyte responses (112). Horvath *et al.* (113) and Horvath and Kovacs (114) have shown that folliculo-stellate cells become activated and increase in size and number in areas of ongoing immune destruction, supporting their role in immune responses.

VIII. Animal Models

Only a few papers have been dedicated to the establishment of animal models of experimental AH. For unknown reasons, the pituitary appears resistant to the experimental induction of disease using the common rodents (mice, rats, and rabbits) and the classical approach that successfully induces experimental encephalomyelitis, thyroiditis, myasthenia gravis, or orchitis (immunization with the antigen of choice emulsified in complete Freund's adjuvant). In 1964 Beutner *et al.* (115) immunized 16 rabbits one to five times with rabbit anterior pituitary extracts, emulsified in complete Freund's adjuvant. They were able to induce specific antibody responses but no pituitary pathology. Levine (116) reported the first successful model of experimental AH, induced by immunizing rats with a single intracutaneous injection of rat pituitary tissue emulsified in complete Freund's adjuvant. The adenohypophysis showed focal and diffuse infiltration 2–3 wk after injection with mononuclear cells (lymphocytes, monocytes, and occasional epithelioid cells) in six of 14 rats (43%). A few posterior and intermediate lobes had minimal inflammation. Disease incidence could be increased to 75% (15 of 20 rats) by addition of a second immunological adjuvant: pertussis toxin. Levine (117) subsequently showed that guinea pig pituitary extracts were the most potent inducer of experimental AH (disease in six of six rat recipients), whereas human and cow extracts were poor inducers, and dog and rabbit extracts were ineffective. In 1970 Beck and Melvin (118) established experimental AH in

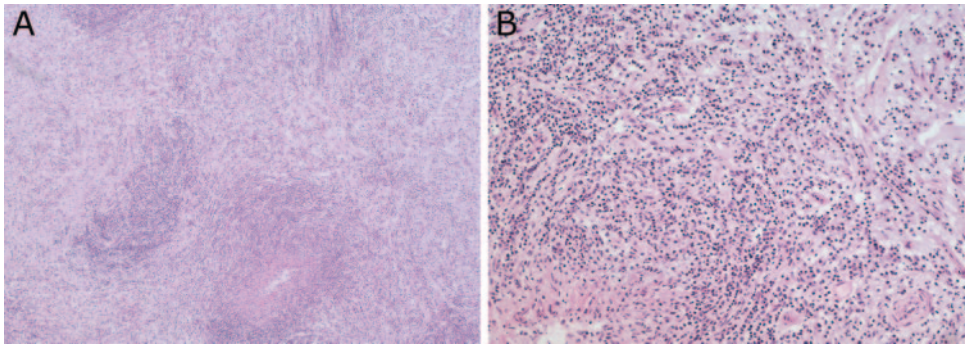

FIG. 3. Histological appearance of the pituitary in AH. The infiltrate disrupts the normal acinar architecture and damages the hormone-secreting cells (A). The infiltrate is mainly mononuclear and composed of lymphocytes and scattered plasma cells (B).

one rhesus monkey by injecting her multiple times, over the course of 3 yr, with human placental extracts and human chorionic gonadotropins, both emulsified in Freund's adjuvant. Histology showed infiltration of the adenohypophysis with lymphocytes and few plasma cells; the neurohypophysis was normal.

In 1982 Klein *et al.* (119) induced lymphoplasmacytic infiltration of the anterior pituitary by injecting 12 rabbits (seven treated and five controls) three times, at 2-wk intervals, with rabbit pituitary tissue emulsified in complete Freund's adjuvant. Eight weeks (10 rabbits) or 16 wk (two rabbits) after the first injection, five of the seven experimental rabbits showed focal infiltration of the adenohypophysis with lymphocytes, some plasma cells, few eosinophils, and fibrosis. None of the five controls showed histological abnormalities. In 1992, Yoon *et al.* (120) immunized more than 100 hamsters by three sc injections of recombinant E1 and E2 glycoproteins from the rubella virus at 1-wk intervals. Specific antibodies against the adenohypophysis were found in 95% of the hamsters 3 wk after the first injection. A diffuse lymphocytic infiltration was seen throughout the adenohypophysis 11 wk after the first injection. None of the hamsters that had received the control protein (nonglycosylated rubella nucleoprotein C) developed such lesions. The disease could be prevented by neonatal thymectomy and could not be produced by passive transfer of the autoantibodies, thus indicating that T cells are critical for disease induction and that antibodies are essentially markers of disease rather than true pathogenic agents (120). Finally, in 2001, Watanabe *et al.* (121) immunized 12 Lewis rats two times, at 1-wk intervals, with rat pituitary extract emulsified in complete Freund's adjuvant. Three weeks (six rats) or 6 wk (six rats) after the first immunization, rats showed minimal lymphocytic infiltration in adenohypophysis and developed antibodies directed against GH, TSH, and LH (121). Overall, histological photographs of the pituitary, reported in four of the seven papers, showed modest or minimal mononuclear infiltration that resembled only remotely the findings observed in the published human cases. In addition, no paper has yet evaluated comprehensively the pituitary function after experimental induction of the disease.

IX. Pathogenic Mechanisms

Criteria used to establish what designates an autoimmune disease have been revisited by Rose and Bona (122) and focus on the issue of whether autoimmunity is the actual cause of disease, rather than a consequence or harmless accompaniment. By this approach, the evidence of autoimmunity is direct, indirect, or circumstantial. Direct evidence requires transmissibility of the characteristic disease lesions from human to human, or from human to animal. This type of evidence, which is mediated by autoantibodies and applicable to some neonatal autoimmune diseases (such as Graves' disease, myasthenia gravis, pemphigus vulgaris, neonatal thrombocytopenia, and neonatal lupus), is lacking for lymphocytic hypophysitis. Pituitary antibodies are present in lymphocytic hypophysitis (see section below), but have not been described to be capable of transmitting disease from mother to newborn. Indirect evidence of an autoimmune etiology is based on the animal models of experimental AH described in the previous section. Circumstantial evidence is the listing of markers descriptive of autoimmune disease. For lymphocytic hypophysitis these markers include improvement of symptoms in response to immunosuppressive drugs (mainly glucocorticoids and, more recently, methotrexate and azathioprine), presence of pituitary autoantibodies, lymphoplasmacytic nature of the histological lesions, and association with other diseases of proven autoimmune nature. In 68 of the 379 patients (18%), AH manifested in patients who had other better-characterized autoimmune diseases, mainly Hashimoto's thyroiditis (28 patients, 7.4%), autoimmune polyglandular syndrome type 2 (seven patients, 1.8%), Graves' disease (six patients, 1.6%), and systemic lupus erythematosus (five patients, 1.3%) (Table 5). Insufficient data are available to establish associations between AH and genes that are classically thought to influence autoimmunity, such as those of the MHC locus and cytotoxic T lymphocyte antigen 4. Also no environmental agent has been linked to AH, with the exception of a few cases presenting after a viral infection of the meninges (57, 123–125). Thus, indirect and circumstantial evidence suggests that lymphocytic hypophysitis is indeed an autoimmune disease.

The autoantigen recognized by the autoimmune infiltrate during AH awaits identification. The laboratory of Kobayashi and associates (126, 127) first described that sera from patients with pituitary disorders, when reacted with pituitary cytosolic extracts, recognized a 22-kDa protein, later identified by Takao *et al.* (128) as GH. Crock's laboratory (129) later reported that seven of 10 patients with biopsy-proven lymphocytic hypophysitis, and 12 of 22 patients with suspected hypophysitis had a low-titer serum antibody directed against a 49-kDa cytosolic pituitary protein, subsequently identified as α-enolase (130). The authors concluded that α-enolase is the autoantigen targeted by the immune system in AH and, considering its coexpression in the placenta, the basis to explain the strong association between AH and pregnancy (131). Antibodies recognizing α-enolase,

TABLE 5. Association between AH and other autoimmune diseases

Associated condition	No. of patients	% of total AH patients
Hashimoto's thyroiditis	28	7.4
APS type 2	7	1.8
Graves' disease	6	1.6
Systemic lupus erythematosus	5	1.3
Sjögren's syndrome	3	0.8
Type 1 diabetes	3	0.8
Optic neuritis	3	0.8
Autoimmune gastritis	2	0.5
Addison's disease	2	0.5
Sarcoidosis	2	0.5
Primary biliary cirrhosis	1	0.3
Myocarditis	1	0.3
Temporal arteritis	1	0.3
Bechet's disease	1	0.3
Erythema nodosum	1	0.3
Rheumatoid arthritis	1	0.3
Idiopathic thrombocytopenic purpura	1	0.3

Association was reported in 67 of the total 376 patients (18%). APS, Autoimmune polyglandular syndrome.

however, have been reported in many other diseases, ranging from endometriosis, to discoid lupus and Wegener's granulomatosis (130). In addition, Tanaka *et al.* (132) have shown that the α-enolase antibody is present in seven of 17 patients (41%) with AH, but similarly in six of 13 (46%) patients with nonfunctioning pituitary adenoma, and in four of 17 (24%) patients with other pituitary diseases, making the α-enolase antibody inadequate as a diagnostic marker of AH. Finally, Nishiki *et al.* (133) reported that five of 13 patients with LAH and one of 12 patients with LINH had antibodies that recognized 68-, 49-, and 43-kDa proteins in pituitary membrane extracts.

It is challenging to speculate on the pathogenesis of the three anatomical forms of AH, and in particular on the genesis of LPH. In LPH, in fact, the immune system theoretically attacks two self-structures, adenohypophysis and neurohypophysis, that, although adjacent, are structurally and embryologically very different. It is possible that the autoimmune process targets simultaneously distinct antigens in the two pituitary lobes, or perhaps the process is initially confined just to the anterior lobe or the posterior lobe and then simply extends to adjacent structures. Animal models will be invaluable in elucidating these different pathogenic mechanisms.

Little is known of the mechanisms by which the infiltrate causes loss of function/destruction of the endocrine cells, or impairment of vasopressin release. The natural history of AH is also incompletely described. It is believed, however, that AH progresses through various stages. Early on, the pituitary is inflamed, infiltrated by lymphocytes, edematous, enlarged, and responsible for the mass effect symptoms; endocrine tests may reveal subclinical hypopituitarism at this stage. If the inflammation resolves, either spontaneously or with the aid of glucocorticoids, and the pituitary parenchyma is not destroyed, remission occurs. If inflammation progresses, the pituitary is replaced by fibrotic tissue and becomes atrophic and loses its function. In keeping with this evolution, imaging studies revealed in 14 AH patients a pituitary mass at diagnosis and an empty sella at some time during follow-up (31, 62, 95, 125, 134–141).

X. Diagnosis

The main diagnostic issue is the distinction between the rare cases of AH and the overwhelmingly more common pituitary tumors, especially nonsecreting adenomas. At the present time, such distinction can be achieved with certainty only by microscopic examination of the pituitary tissue obtained from surgery. Even when using modern magnetic resonance imaging (MRI) studies, approximately 40% of the cases are misdiagnosed preoperatively as pituitary adenomas (58). Authors have strived, however, to define presurgical criteria suggestive more of AH than adenoma. These criteria include clinical features, endocrinological assessment, immunological markers, and imaging studies.

A. Clinical features

Clinical suspicion of AH should be raised if symptoms appear in striking temporal relationship with pregnancy and postpartum, and if the degree of hypopituitarism (partial or complete) appears disproportionate to the relatively small size of the radiologically shown pituitary mass (142). It was also originally proposed (47) that in AH the hypopituitarism involves mainly the adrenal and thyroidal axis, a possibly useful criterion to differentiate AH from pituitary macroadenomas in which the hypopituitarism usually begins with reduced levels of gonadotropins and GH (143). This proposal, however, does not completely hold when larger numbers of patients are analyzed (see *Section X.B.* and Table 6), considering that gonadotrophs are as equally impaired as the thyrotrophs. Overall, clinical criteria have extremely low predictive values and do not characterize the presentation of AH, which is usually indistinguishable from that of any expanding mass located in the sella turcica.

B. Endocrinological assessment

Evaluation of the anterior pituitary function at presentation shows that, in LAH, the cells most frequently impaired are the corticotrophs (56% of patients), followed by thyrotrophs and gonadotrophs (~43%), and lastly by somatotrophs and lactotrophs (~25%) (Table 6). Based on these data and the notion that ACTH deficiency can be observed in isolation (144, 145), some authors consider ACTH deficiency the earliest functional alteration in AH. This propensity for ACTH deficiency may indicate that the initial autoantigen/s targeted by the immune system reside within the corticotrophs. It is important to note, however, that isolated

TABLE 6. Endocrine assessment of pituitary function at presentation in patients with LAH, LINH, or LPH

	LAH (n = 245)	LINH (n = 38)	LPH (n = 95)
Adrenal axis			
Pituitary defect	136 (56)	0	44 (46)
Adrenal defect	8 (3)	0	0
Normal	56 (23)	33 (84)	34 (36)
Not recorded	45 (18)	6 (16)	17 (18)
Thyroidal axis			
Pituitary defect	107 (44)	0	37 (39)
Thyroid defect	27 (11)	0	8 (9)
Normal	62 (25)	34 (87)	35 (37)
Increased	6 (2)	0	0
Not recorded	43 (18)	5 (13)	15 (16)
Gonadal axis			
Pituitary defect	104 (42)	3 (8)	45 (47)
Gonadal defect	2 (1)	0	0
Normal	72 (29)	30 (77)	33 (35)
Not recorded	67 (27)	6 (15)	17 (18)
GH			
Decreased	63 (26)	0	48 (51)
Normal	76 (32)	31 (79)	25 (26)
Increased	4 (1)	8 (21)	0
Not recorded	100 (41)	0	22 (24)
PRL			
Decreased	62 (25)	0	15 (16)
Normal	75 (31)	28 (72)	29 (30)
Increased	57 (23)	5 (13)	38 (40)
Not recorded	51 (21)	6 (15)	13 (14)
ADH			
Decreased	0	38 (98)	90 (95)
Normal	47 (19.2)	0	5 (5)
Increased	1 (0.4)	0	0
Not recorded	197 (80.4)	1 (2)	0

Data represent number of patients, with percentages in *parentheses*.

ACTH deficiency can be observed in the absence of AH (146, 147), and that isolated deficiencies of other anterior pituitary hormones have been described in AH (148). The greater frequency of ACTH deficiencies may simply represent an ascertainment bias, considering that these patients may come to medical attention more readily than patients with other adenohypophyseal hormone deficiencies.

GH is most frequently normal in LAH and LINH (Table 6), although it was not evaluated in a discrete percentage of patients. If confirmed, however, the normal GH finding could be helpful to distinguish AH from other underdiagnosed causes of hypopituitarism, such as pituitary apoplexy, radiation-induced hypopituitarism (149), and hypopituitarism following traumatic brain injury (150, 151). In these three conditions, in fact, GH deficiency is the most common manifestation of pituitary dysfunction.

Pituitary apoplexy is an acute clinical syndrome consisting of the sudden onset of headache, visual disturbances, ophthalmoplegia, nausea, vomiting, and altered mental status (152). It results from a sudden increase in the size of the pituitary gland secondary to hemorrhagic infarction and occurs primarily in patients with preexisting pituitary adenoma. In AH the onset is rarely so acute, but cases have been described that present as pituitary apoplexy (153, 154). Even more challenging is the distinction between AH associated with pregnancy and the pituitary apoplexy that occurs postpartum (Sheehan syndrome). Sheehan syndrome results from the hypotension secondary to severe uterine hemorrhage at the time of delivery and causes necrosis of the anterior pituitary with subsequent organization and scar formation (155). The clinical picture is usually that of a gradually evolving hypopituitarism, which, however, may remain undetected for years. In addition, pituitary antibodies have been described in Sheehan syndrome (156), and its histological appearance can be similar to that of late-stage, fibrous AH (155).

C. Immunological markers

In AH, as in most other autoimmune diseases, the clinical immunology laboratory assesses, at present, only the function of B lymphocytes (*i.e.*, antibody levels), although T lymphocytes are likely more critical for disease development. Antibodies against pituitary antigens have been measured mainly by indirect immunofluorescence (157) or immunoblotting (158) and only in one patient by ELISA (159). In immunofluorescence, which is labor intensive and difficult to standardize, the patient's serum is reacted with frozen sections prepared from pituitary substrates of various sources: human surgical specimens (157), human fetuses (160), primate pituitaries (157), rodent pituitaries (161), rat GH3 cell line (162), and mouse AtT20 cell line (163). Immunofluorescence was used in 62 AH patients and reported positive only in 16, suggesting a sensitivity of 26%. Even when the analysis is restricted to LAH patients, the sensitivity remains low: 14 true positive of 39 patients assayed (36%) (Table 7). The specificity of pituitary antibodies is poor, as they have been found in various nonautoimmune pituitary diseases such as Cushing's disease (160), pituitary adenomas (164), empty sella syndrome (165), and Sheehan syndrome (156), as well as in other autoimmune diseases such as type 1 diabetes (166), Hashimoto's thyroiditis (167), and Graves' disease (161).

TABLE 7. Pituitary antibody results in patients with LAH, LINH, or LPH

	LAH (n = 245)	LINH (n = 39)	LPH (n = 95)
Not measured	190	32	70
Measured by immunofluorescence	39	4	19
Negative	25	5	17
Positive	14 (36%)	0	2 (10%)
Measured by immunoblotting	16	3	5
Negative	5	2	1
Positive	11 (68%)	1 (33%)	4 (80%)
Measured by ELISA	0	0	1
Negative			1
Positive			0

In immunoblotting, cytosolic or membrane proteins are extracted from normal pituitary glands, fractionated by size in the electrophoretic field, blotted to a solid support, and reacted with the patient's serum. Immunoblotting was used in 24 AH patients and showed reactivity for cytosolic and/or membrane pituitary proteins in 16 patients, providing a better sensitivity than immunofluorescence (67%) (Table 7). There was poor correlation between the presence of pituitary antibodies and a corresponding pituitary hormone deficiency (52).

Taken together, human studies and animal models suggest that pituitary antibodies, as measured by current assays, are associated with AH; their role in the pathogenesis of AH, however, remains to be established.

D. Imaging studies

Computer-assisted tomography, obtained in the first AH patient diagnosed ante mortem (41), was the only available cross-sectional imaging technique until 1988. Since that time, MRI has become the procedure of choice because it has distinct advantages over computer-assisted tomography for imaging the pituitary gland. MRI, in fact, is usually safer (no ionizing radiation), easier to perform (no need for extended neck), achieves excellent spatial resolution, has superior soft tissue contrast, provides a panoramic view of the sellar region (optic nerves and intracranial compartments), and allows fast, dynamic, contrast-enhanced imaging. MRI of the pituitary is performed with high-field strength units, high resolution (usually 1 mm slice thickness), and dynamic technique in which images are obtained during contrast administration.

On precontrast T1-weighted images, the normal adenohypophysis demonstrates a homogenous signal, approximately isointense to the gray matter, whereas the normal neurohypophysis is hyperintense. The hyperintensity of the neurohypophysis is believed to reflect the high phospholipid content of the ADH and oxytocin neurosecretory granules (168). After gadolinium, there is a physiological, homogeneous enhancement of the entire gland that renders the anterior and posterior lobes indistinguishable.

Pituitary size is routinely estimated using the vertical diameter (height), which should not exceed 6 mm in children,

8 mm in men, and 10 mm in nonpregnant women (66). Pituitary sizes increases during pregnancy and decreases in the elderly. In the elderly, small glands are normal and often associated with the presence of cerebrospinal fluid within the sella, a condition called "empty sella," which by itself is not predictive of pituitary pathology.

In LAH the typical precontrast MRI findings include a symmetric enlargement of the pituitary gland, a thickened but rarely displaced stalk, and a usually intact sellar floor (135, 169, 170). By contrast, pituitary macroadenomas are asymmetric, displace the infundibular stalk, depress or erode the sellar floor, and only rarely obscure the posterior pituitary hyperintensity (Table 8). Another feature more suggestive of LAH is the precontrast homogeneity of the pituitary mass. Macroadenomas, by contrast, whether secreting or not, whether benign or malignant, often develop cystic areas (that appear as low signal intensity on T1- and high signal intensity on T2-weighted images), or hemorrhages (that cause high signal intensity on both sequences). Glandular homogeneity, however, is not specific for LAH because a cystic appearance was described in 12 of the total 250 patients in whom MRI was performed (5%), all 12 cases being histologically proven primary LAH (56, 124, 137, 171–177). The largest series in this regard is that by Flanagan *et al.* (175) who reported five patients with LAH, three of whom had cystic changes of the pituitary on MRI.

The pattern of signal enhancement after gadolinium may be helpful in differentiating LAH from macroadenoma. A strong and homogenous enhancement of the anterior pituitary, similar to the cavernous sinus, is more suggestive of an inflammatory infiltrative process such as LAH rather than a macroadenoma (135, 178). Macroadenomas, in fact, enhance less or more slowly than the normal pituitary on dynamic MRI. Unfortunately, strong and homogenous enhancement can also be observed in pituitary adenomas that develop secondary inflammatory changes (32). Essentially, unless there is avid enhancement similar to the cavernous sinus, the differentiation between LAH and atypical adenoma is tenuous. Some authors have described in LAH strips of contrast enhancing tissue along the dura mater (so called, "dural tail" or "meningeal tail") (178), a nonspecific finding that is classically observed in intracranial meningiomas (179).

In LINH there is the loss of T1 hyperintensity in the neurohypophysis (180). Various infiltrative, inflammatory, or neoplastic processes can, however, produce that same finding, making it not specific for LINH. In addition, such hyperintensity may be absent in as much as a third of normal elderly subjects (181). Two additional radiological features of LINH include swelling of the posterior pituitary and thickening of the pituitary stalk greater than 3 mm at the level of the median eminence of the hypothalamus (182). After administration of gadolinium, the stalk and the posterior pituitary enhance rapidly and avidly because of their rich capillary network. Sato *et al.* (183) used dynamic MRI in five AH patients with involvement of the posterior lobe and reported a delayed, or absent, early enhancement of the neurohypophysis.

In summary, the MRI findings are not specific enough to distinguish with certainty AH from the more common pituitary adenomas. However, the symmetry of pituitary enhancement, the lack of erosive changes of the sellar floor, the homogeneity of the pituitary mass, and its intense enhancement after gadolinium can be diagnostic in the proper clinical context. Careful correlation with clinical history and endocrine findings is therefore important for a proper interpretation of the MRI findings in AH.

TABLE 8. MRI findings in LAH and pituitary macroadenomas

	LAH	Macroadenoma
Asymmetric mass	−	+
Precontrast homogeneous signal	+	−
Intact sellar floor	+	−
Suprasellar extension	+	+
Stalk thickening	+	−
Stalk displacement	−	+
Homogeneous enhancement	+	−
Loss of posterior hyperintensity[a]	+	−

+, More common; −, less common.
[a] Seen when the infundibuloneurohypophysis is involved.

XI. Treatment and Outcome

The treatment of AH is, at the moment, only symptomatic. It includes reducing the size of the pituitary mass and/or replacing the defective endocrine function. Mass reduction can be achieved by pituitary surgery, lympholytic drugs (glucocorticoids, azathioprine, or methotrexate), or radiotherapy.

Surgery has been the most common form of treatment in AH, being performed in 243 (64%) of the total 379 patients reported thus far. It aims to reduce the pituitary mass and the associated compressive effects on the surrounding structures, without introducing new endocrine or neurological deficits. Surgery is usually performed via the endonasal transphenoidal approach, which requires only minimal resection of the mucosa, rarely by craniotomy. Lately, an endoscopic endonasal transphenoidal surgery has been developed with the goal of diminishing surgical invasiveness even further. In a series of 160 patients, Jho (184) reported that endoscopic transphenoidal surgery provided comparable surgical outcomes to conventional microscopic transphenoidal surgery. Subsequently, Cappabianca *et al.* (185) have shown in 100 consecutive patients with pituitary tumors that the endoscopic technique also results in a reduced number of complications. As with many other surgical procedures, and regardless of the traditional or endoscopic approach, outcome improves when surgery is performed at high-volume hospitals and by high-volume surgeons (186).

Surgery, in addition to providing a histological diagnosis, is very effective in achieving decompression of the sellar mass and thereby promptly resolving headaches and visual deficits. Only rarely, however, does it improve the preexisting endocrine defects. Surgery can also cause complications such as bleeding, cerebrospinal fluid leaks, and diabetes insipidus, which are often transitory but occasionally recalcitrant. The role of surgery in the definitive treatment of AH remains controversial, but current literature suggests restricting its indications. When the preoperative diagnosis of a pituitary mass is still undefined, surgery should be per-

formed only in the presence of serious and progressive deficits of visual fields, visual acuity, or ocular movements, not responsive to medical treatment. Patients presenting with hypopituitarism, diabetes insipidus, or hyperprolactinemia rarely benefit from surgery because their defects are secondary to diffuse lymphocytic infiltration, rather than to compression of the normal parenchyma that surrounds the pituitary mass. Based on this rationale, if surgery is performed and intraoperative histology on frozen sections suggests AH, the surgeon should try to achieve decompression of the osseous sella turcica rather than extensive debulking of the lesion, as is the objective for pituitary adenomas.

Glucocorticoids can be effective for treating AH, both as antiinflammatory agents to reduce the size of the pituitary mass or the thickened stalk, and as replacement of defective adrenal function. The most commonly used glucocorticoids have been prednisone (from 20 to 60 mg/d) (187–189), hydrocortisone (63, 65), and methylprednisolone (120 mg/d for 2 wk) (139, 190–193). Kristof *et al.* (139) performed the first and only prospective trial of glucocorticoid use in nine patients with AH. They showed that methylprednisolone improved adenopituitary function in four patients and MRI appearance in seven patients. Considering the absence of a control group and randomization, it is difficult to conclude that glucocorticoids are preferable (125). In addition, the occurrence of spontaneous recovery can be a confounder (188). It seems reasonable, however, to advocate the use of glucocorticoids, rather than surgery, as the first line of treatment. If the pituitary mass is truly AH, it should be reduced upon glucocorticoid treatment because of their well-known lymphocytolytic properties. Indeed, response to glucocorticoid therapy, measured as volume reduction of the pituitary mass and improvement of the hormonal status, may help to confirm the diagnostic suspicion of AH. Dose and requirement of glucocorticoids vary with disease stage, and it is likely that fibrous stages of AH will be unresponsive to glucocorticoids. More recently, other immunosuppressive drugs, such as azathioprine (192) and methotrexate (58, 93), were used in patients who responded poorly to glucocorticoids.

Pituitary radiotherapy, either the conventional fractionated external-beam radiotherapy or the more recent γ-knife radiosurgery, has long been part of the therapeutic armamentarium for managing tumors derived from the sellar region. Radiotherapy was used successfully in two cases of AH (one pathologically proven) that were unresponsive to surgery or glucocorticoids (194). Controversy still exists, however, on the applications of pituitary radiotherapy and the true clinical relevance of its quoted complications (195).

In summary, two main approaches have been used to treat AH patients who present with symptoms of sellar compression: surgical removal of the infiltrated pituitary (31, 55, 57) or supraphysiological doses of glucocorticoids (188, 196). Current literature favors to begin with the second approach (58). If a diagnosis of AH is suspected based on clinical and radiological criteria and there are no urgent visual disturbances requiring surgical decompression, clinicians should first try to reduce the pituitary mass pharmacologically, while monitoring the patient's endocrine status and pituitary MRI morphology. If symptoms persist or worsen, or the patient does not tolerate high-dose glucocorticoids, then transphenoidal surgery should be performed.

Follow-up information was available in the majority of patients (320 of 379; 84%), although follow-up time was overall short (median, 1.3 yr; interquartile range, 2 yr; minimum to maximum range, 0.08 to 11 yr). Most patients (233 of 320; 73%) required long-term replacement with one or more hormones (Table 9). Recovery was unusual after transphenoidal surgery, and seven patients required a second surgery to reduce the recurring pituitary mass (57, 175, 194, 196, 197). In 51 of 320 patients (16%), AH resolved after mass-reducing treatment without the need of hormone replacement. Twenty-five patients with AH (8%) died, presumably from irreversible adrenal insufficiency. Deaths have been reported at a constant rate through the years (11 deaths from 1962–1982 and 14 deaths from 1983–2004), suggesting that mortality from AH has not improved despite improved technology. Finally, in 11 patients (3%), AH resolved spontaneously without any treatment. This latter observation suggests that asymptomatic cases may exist and that the prevalence of AH is higher than what is currently estimated.

XII. Importance of a Disease Registry

Applying the previously discussed AH incidence estimate of 1 per 9 million/yr to the U.S. population (281,421,906 based on census 2000 data), only 31 new cases of AH would be anticipated each year. Given the rarity of this disease, the establishment of a research registry has obvious benefits, which have been duly noted in the Autoimmune Disease Research Plan (198) prepared by the National Institutes of Health Autoimmune Diseases Coordinating Committee. Without some means of pooling cases, it is difficult for researchers to assemble study populations of sufficient size to conduct statistically meaningful research. A registry would thus serve as a source of well-characterized cases for both basic science and clinical research, fostering innovation in the

TABLE 9. Follow-up (FU) status of patients with LAH, LINH, or LPH

	LAH (n = 245)	LINH (n = 39)	LPH (n = 95)	No. of patients where FU was available (n = 320)
Required long-term hormone replacement	137	27	69	233 (73%)
Improved after mass reduction, without need for hormone replacement	38	3	10	51 (16%)
Death	21	2	2	25 (8%)
Resolved spontaneously	11	0	0	11 (3%)
No FU available	38	7	14	

field. The registry would begin with participation from leading referral hospitals for AH treatment but ideally could put in place protocols for case submission from smaller institutions. It could conceivably include biological (*e.g.*, blood, tissue samples) as well as clinical data. The registry would permit active follow-up, updating information about survival and quality of life. It could also arrange for consent upon enrollment to permit patients to participate in special studies requiring additional data collection. Readily adaptable models for such a research registry already exist in the Rare Disease Registry Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, which funds registries for ichthyosis, juvenile rheumatoid arthritis, new-onset juvenile dermatomyositis, and neonatal lupus. The impact of such disease registry is high, as shown, for example, by the neonatal lupus registry (199).

XIII. Concluding Remarks and Future Perspectives

AH is rare but increasingly recognized. It should be considered in the differential diagnosis of any nonsecreting pituitary mass, especially if presenting during pregnancy or postpartum. In the absence of surgical emergency, such as impending loss of vision, medical management combined with sequential MRI is preferable, although this approach precludes the definitive pathological diagnosis. Patient management will be improved when a robust immunological diagnostic test becomes available. Much remains to be learned about the natural history of AH, which ranges from spontaneous recovery to death. Establishment of animal models and a disease registry could provide an improved understanding of AH and a method of preoperative diagnosis.

AH offers a fascinating model with which to elucidate the effect of pregnancy on autoimmune diseases and the interactions between nervous, endocrine, and immune systems. We do not know of any other autoimmune disease that is modulated in such a dramatic fashion by pregnancy. Understanding the gestational changes in the immune system that determine the appearance of AH may have therapeutic significance, not only for AH but also for other more common autoimmune diseases.

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