From Pituitary Expansion to Empty Sella: Disease Progression in a Mouse Model of Autoimmune Hypophysitis

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Lymphocytic hypophysitis has a variable clinical course, where a swelling of the pituitary gland at presentation is thought to be followed by pituitary atrophy and empty sella. Data in patients, however, are scanty and contradictory. To better define the course of hypophysitis, we used an experimental model based on the injection of pituitary proteins into SJL mice. A cohort of 33 mice was divided into three groups: 18 cases were immunized with pituitary proteins emulsified in complete Freund’s adjuvant; six controls were injected with adjuvant only; and nine controls were left untreated. Mice were followed by cranial magnetic resonance imaging (MRI) for up to 300 d, for a total of 106 MRI scans, and killed at different time points to correlate radiological and pathological findings. Empty sella was defined as a reduction in pituitary volume greater than 2 SD below the mean volume. All immunized mice showed by MRI a significant expansion of pituitary volume during the early phases of the disease. The volume then decreased gradually in the majority of cases (14 of 18, 78%), reaching empty sella values by d 300 after immunization. In a minority of cases (four of 18, 22%), the decrease was so rapid and marked to induce a central area of necrosis accompanied by hemorrhages, mimicking the condition known in patients as pituitary apoplexy. No radiological or pathological changes were observed in controls. Overall, these findings indicate that the evolution of hypophysitis is complex but can lead, through different routes, to the development of empty sella. (Endocrinology 152: 4190–4198, 2011)
the pituitary gland. It can be mimicked experimentally in the mouse by immunization with pituitary proteins (4). Granulomatous hypophysitis has been reported in over 120 patients since 1908. It features multinucleated giant cells that organize in granulomas with palisading histiocytes surrounded by T cells and plasma cells (5). Xanthomatous hypophysitis, described in 13 patients since 1998, displays foamy histiocytes and macrophages, accompanied by plasma cells and lymphocytes (6). Necrotizing hypophysitis, reported in three patients since 1993, is characterized by mononuclear infiltration within a pituitary tissue that shows significant nonhemorrhagic necrosis (7). Finally, IgG4-related hypophysitis, the most recent addition to the hypophysitis spectrum, described in 13 patients since 2004, is characterized by a mononuclear infiltration of the pituitary gland containing more than 10 IgG4-producing plasma cells per high-power field, usually accompanied by IgG4-positive lesions in other organs (8).

The natural history of hypophysitis is variable, ranging from complete resolution to death (1, 9). The majority of patients (65%) require some form of long-term hormone replacement; other patients (20%) improve after mass-reducing treatments (such as pituitary surgery or high-dose glucocorticoids) without need of hormone replacement; some patients (10%) die because of hypophysitis and are diagnosed at autopsy; in a minority of cases (5%), hypophysitis is aggressive and recurs after the initial mass-reducing treatment, so that a second surgery is necessary to alleviate the mass-effect symptoms. Part of this variability is explainable by differences in the modality and length of the follow-up, which overall tends to be short (less than 2 yr after diagnosis) in the majority of published patients. Morphologically, the pituitary gland is typically enlarged at presentation and likely shrinks during follow-up. Some authors have also reported by magnetic resonance imaging (MRI) a loss of intrasellar volume and secondary empty sella (10).

Empty sella is a herniation of the subarachnoid space into the sella turcica, leading to stretching of the stalk and flattening of the pituitary gland against the sellar walls (11). The term empty sella was originally used at autopsy to describe the appearance of the sellar region in patients with postpartum pituitary necrosis (12) but is nowadays a neuroradiological diagnosis. Morphologically, empty sella is classified into total, when more than 50% of the sella is filled with cerebrospinal fluid and the pituitary gland thickness is less than 2 mm, or partial, when less than 50% is filled and the pituitary thickness is at least 3 mm (13). Mechanistically, empty sella recognizes primary and secondary forms. Primary empty sella associates with congenital anatomic variations of the sellar diaphragm that are typically discovered incidentally, or with suprasellar causes that lead to increases in intracranial pressure (14). Secondary empty sella, on the contrary, is caused by a loss of pituitary volume. This loss can be seen after extensive pituitary surgery, after prolonged pituitary radiotherapy, in Sheehan syndrome (ischemic necrosis after peripartum hemorrhages), or in pituitary adenomas that undergo hemorrhagic necrosis (pituitary apoplexy). Hypophysitis is a potential cause of secondary empty sella if it is true that the pituitary gland targeted by autoimmunity becomes atrophic with time.

Given the rarity of hypophysitis, the paucity of prolonged follow-up times, and the fact that most patients undergo some forms of mass reduction (thus preventing observation of a bona fide natural history), it remains uncertain whether empty sella is indeed a final outcome of autoimmune hypophysitis. The goal of this study was to characterize by MRI the evolution and late course of lymphocytic hypophysitis using a previously developed mouse model of the disease (4).

**Materials and Methods**

**Study design and immunization scheme**

The study used a cohort of 33 SJL/J female mice (from The Jackson Laboratory, Bar Harbor, ME) distributed into three groups. Cases (n = 18) were immunized twice (on d 0 and 7, corresponding to ages of 63 and 70 d) using 0.5 mg mouse pituitary cytosolic proteins emulsified in complete Freund’s adjuvant, according to the protocol previously described (4). Controls included six age-matched mice that received on d 0 and 7 only the complete Freund’s adjuvant without pituitary proteins (CFA controls), and nine age-matched mice that were left untreated (nonimmunized controls). All experimental procedures were approved by the Animal Care and Use Committee of the Johns Hopkins University School of Medicine.

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**TABLE 1.** Distribution of the MRI studies (n = 106) according to age (in days) and experimental group.
MRI studies used to describe the normal mouse pituitary volume.

In vivo MRI of the mouse brain

MRI was performed using a horizontal 9.4-Tesla nuclear magnetic resonance spectrometer (Bruker Biospin, Billerica, MA) and a 40-mm-diameter birdcage coil as radio frequency transmitter and receiver. Mice were anesthetized using 1% isoflurane in a mixture of 75% air and 25% oxygen and placed in a custom-designed head holder with ear pins and nose cone to restrain head motion. Respiration was monitored using a small-animal imaging system (SA instruments, Inc., Stony Brook, NY) and kept at a rate of approximately 60–80 breaths per minute. T1-weighted images were acquired using a two-dimensional multiple-slice spin echo sequence, with an echo time of 11 msec, a repetition time of 500 msec, in-plane resolution of 0.1 mm × 0.1 mm, 24 coronal slices with 0.3-mm slice thickness, and 10 signal averages. Image reconstruction was performed on the spectrometer console (Paravision, version 3.0.2; Bruker Biospin). Two of 33 mice (6%) died toward the end of the MRI procedure because of the anesthesia.

Pituitary histopathology

Immunized mice were killed at sequential time points to correlate the pituitary MRI findings with pathological changes. Pituitary glands were fixed overnight in Beckstead’s solution, embedded in paraffin, and processed as described (4). Sections were stained with hematoxylin and eosin for morphology and Mason’s trichrome for fibrosis. Sections were scored qualitatively by three investigators (S.C.T., M.L.S., and P.C.).

Statistical analysis

The study analyzed four outcomes: pituitary volume (Figs. 1–3), pituitary histopathology (Fig. 4), pituitary signal intensity before and after Gd (Figs. 5 and 6), and pituitary antibodies (Fig. 7).

Statistical analysis was performed using the nonparametric Wilcoxon rank sum test. After Gd injection, the intensity at the various time points was averaged and then normalized to the intensity of the cerebral cortex, which does not vary with Gd due to the presence of the blood-brain barrier. Averaged and normalized intensity of the anterior and

### TABLE 2. Distribution of the MRI studies (n = 106) according to the day after immunization and experimental group

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CFA, Complete Freund’s adjuvant. Numbers in **bold** refer to the 32 MRI studies used to describe the normal mouse pituitary volume.

**FIG. 1.** Pituitary volume in normal (not immunized) mice. A, Total pituitary volume (anterior plus posterior lobe) throughout the lifetime. Note the significant increase from 50–60 d of age. B, Distribution of total pituitary volume in adult (>60 d) mice. The **thick line** shows the kernel density estimate of the volume based on the mean and SD of 22 MRI scans. The **thin line** reports the normal density that would be obtained based on the same mean and SD. The **dotted lines in both panels** represent the mean plus 2 SD and the mean minus 2 SD values of the total pituitary volume distribution.

**FIG. 2.** Normal adult pituitary volume. A, Normal pituitary volume (mm³) age at MRI (days). B, Kernel density estimate of the normal adult pituitary volume. The **thick line** represents the kernel density estimate of the normal adult pituitary volume, and the **thin line** reports the normal density that would be obtained based on the same mean and SD. The **dotted lines** represent the mean plus 2 SD and the mean minus 2 SD values of the normal adult pituitary volume distribution.
posterior lobe were then compared among groups by the Wilcoxon rank sum test.

Pituitary antibodies followed a nonnormal distribution and were thus natural log-transformed to satisfy assumptions of normality and equal variances. Results were then analyzed by multiple linear regression to assess changes in antibody levels according to age and pituitary volume.

Statistical analyses were performed using Stata statistical software, release 10 (StataCorp LP, College Station, TX).

Results

Normal pituitary volume

In normal (nonimmunized) mice (N = 32), the total volume of the pituitary gland increased significantly from 50–60 d of age (P = 0.001, Fig. 1A, closed circles), a period corresponding to completion of puberty and sexual maturation. This increase was due exclusively to the anterior pituitary (Fig. 1A, open diamond) because the posterior pituitary remained largely unchanged throughout life (Fig. 1A, closed diamond). In adult (>60 d of age) mice (N = 25), the total pituitary volume had a mean of 2.47 mm$^3$ and SD of 0.26 mm$^3$ and followed a normal distribution (Fig. 1B). Volumes greater than 2.98 mm$^3$ (mean + 2 SD) were considered indicative of pituitary enlargement, and volumes smaller than 1.69 mm$^3$ (mean - 3 SD) indicative of pituitary atrophy and empty sella. The mean (SD) of adult anterior and posterior pituitary volumes were 2.23 (0.26) and 0.23 (0.08) mm$^3$, respectively.

Pituitary volume after immunization

Immunization with pituitary proteins, begun after 60 d of age, markedly modified the pituitary volume. Volume became significantly greater than baseline on d 20 (3.37 ± 0.8 mm$^3$, P = 0.0003 vs. d 0, Fig. 2A, white circle) and peaked 1 month after immunization (3.75 ± 1.9, P < 0.001 vs. d 0, Fig. 2A, white diamond). Volume then remained significantly larger than baseline on d 40, 70, 100, and 140 after immunization, started to decrease on d 175, and approached baseline values on d 225 (1.9 ± 0.68). On d 300, volume became significantly smaller than baseline, reaching atrophic values (1.08 ± 0.38, P < 0.0001 vs. d 0, Fig. 2A). Pituitary volume varied significantly during the initial phase of hypophysitis (first month after immunization), a variation partly explainable by two distinct patterns of radiological and morphological lesions.

Lymphoid form

The majority of immunized mice (14 of 18, 78%) developed a clear initial enlargement of the pituitary gland followed by a gradual and slow decline toward atrophy (Fig. 2B). The initial enlargement was clearly detectable by MRI (Fig. 3B) and sustained pathologically by a diffuse lymphocytic infiltration of the adenohypophysis (Fig. 4B). At later stages, the pituitary gland became markedly atrophic (Fig. 3C) and showed prominent fibrosis (Fig. 4C) in addition to the lymphocytes that remained the predominant hematopoietic cell type throughout the course of the
disease. At these later stages, the anterior pituitary displayed dense, interlacing bands of fibrosis (turquoise staining in Fig. 4C), demarking small areas of atrophic pituitary cells, overall resembling a sort of hypophyseal cirrhosis.

**Apoplectic form**

In the remaining minority of immunized mice (four of 18, 22%), the initial expansion of the pituitary was so rapid it induced a central area of necrosis accompanied by extravasation of blood from the vessels (Figs. 3D and 4D). This form of hemorrhagic necrosis caused a rapid increase in pituitary volume followed by a brisk, rather than gradual, decrease (Fig. 2C). It mimics closely a condition known in patients as pituitary apoplexy that, although more often described in pituitary adenomas, has also been reported in lymphocytic hypophysitis (15–20).

The above-described changes in pituitary volume were exclusively seen in the adenohypophysis. The posterior pituitary volume remained unchanged after immunization, in keeping with the lack of lymphocytic infiltration in the posterior pituitary (data not shown). Its volume was 0.207 mm³ in all groups, with a similar SD around 0.05.

Pituitary volume assessed by MRI correlated strongly with postmortem pituitary weight [Pearson correlation coefficient (r) of 0.895], so that it could be used to predict weight in a univariate linear regression analysis: for every unit (cubic millimeter) increase in pituitary volume, the pituitary weight increased 0.8576 mg (95% confidence interval, 0.63–0.87; P < 0.0001).

**Pregadolinium T1 signal intensity**

Before gadolinium, the mean ± SD T1 signal intensity of the anterior pituitary gland was similar in immunized (1.11 ± 0.07) and control mice (1.15 ± 0.05, P = 0.145 by Wilcoxon rank sum test, Fig. 5A, black boxes) and did not correlate with anterior pituitary volume (data not shown), overall suggesting that precontrast signal intensity does not discriminate normal pituitary from hypophysitis.

Before gadolinium, the T1 signal intensity of the posterior pituitary in un-
immunized mice was significantly higher than that of the anterior pituitary (1.53 ± 0.06, P = 0.0001, Fig. 5A), mimicking the bright spot observed in human pituitary glands. After immunization, the precontrast posterior pituitary bright spot remained (1.57 ± 0.18, P = 0.0001 vs. anterior pituitary, Fig. 5A) and was not different from the one observed in unimmunized controls.

Peak postgadolinium T1 signal intensity
After gadolinium, the peak ± SD T1 signal intensity of the anterior pituitary gland was significantly higher in the immunized group (1.97 ± 0.23) than in controls (1.78 ± 0.13, P = 0.0016 by Wilcoxon rank sum test, Fig. 5B, black boxes). The intensity was directly proportional to the anterior pituitary volume during the initial disease phase (regression coefficient 2.73, P = 0.015), but not after 120 d after immunization. Overall, these data suggest that gadolinium-enhanced images distinguish hypophysitis from normal pituitary if acquired early during disease development.

After gadolinium, the peak (mean ± SD) T1 signal intensity of the posterior pituitary was similar in immunized (2.39 ± 0.15) and control (2.36 ± 0.20) mice.

Dynamic postgadolinium T1 signal intensity
T1 MRI images were acquired 10, 20, 30, 40, 50, 60, and 70 min after gadolinium administration to characterize the dynamic of contrast uptake. The T1 intensity tended to peak at 40 min, but overall, it was not significantly different from the other time points, both in controls (Fig. 6A) and immunized mice (Fig. 6B).

Pituitary antibodies and pituitary volume
Pituitary antibodies, not surprisingly, higher in immunized mice (Fig. 7A, circles) than in unimmunized controls (Fig. 7A, diamonds), declined gradually with age but remained higher than controls for up to 1 yr after immunization. Antibodies correlated directly with pituitary volume, being higher in mice with larger pituitary volumes and lower in smaller volumes (Fig. 7B), in keeping with the notion that autoantibodies decline with decreasing antigenic loads (21). In particular, for every unit increase in the log of pituitary antibodies, the volume increased 1.10 mm³ (95% confidence interval, 0.48–1.73; P = 0.002).

Discussion
We report in a mouse model of lymphocytic hypophysitis that progression toward pituitary atrophy and empty sella is the final outcome of this disease. Empty sella was reached gradually over the course of several months in the majority of mice, or abruptly in those that developed pituitary apoplexy. The study thus contributes to the understanding of an aspect of hypophysitis that in humans remains difficult to ascertain. First of all, because a diagnosis of certainty of hypophysitis depends upon surgical intervention, the natural history of the disease cannot be ob-

FIG. 5. MRI signal intensity of the mouse pituitary. A, Intensity before gadolinium (Gd) administration. Note that the posterior pituitary (gray boxes) is significantly brighter than the anterior pituitary (black boxes). The baseline intensity of both the anterior and posterior pituitary does not change after immunization. B, Intensity after Gd administration. The posterior pituitary retains its inherent stronger brightness but is unaffected by immunization. The anterior pituitary becomes brighter after Gd, and more significantly so in immunized mice. NS, Not significant.

FIG. 6. Dynamic T1 pituitary intensity after Gd administration in controls (A) and immunized (B) mice. Note the small variation around the mean T1 signal intensity after Gd injection in immunized mice.
served. More importantly, the follow-up is often incompletely reported or short. When coupled with the rarity of hypophysitis, these aspects make it difficult to reach firm conclusions.

Review of the hypophysitis literature for the presence of an empty sella identified 27 patients, 10 biopsy proven (all lymphocytic) and 17 clinically suspected (Supplemental Table 1, published on The Endocrine Society’s Journals Online web site at http://endo.endojournals.org). The first case was reported in 1986 by Okada et al. (22) in a 28-yr-old woman with clinically suspected hypophysitis and pituitary antibodies who developed empty sella 2 yr after diagnosis. Empty sella was present at diagnosis in two patients (23, 24) and reported at some time during follow-up in the remaining 25 cases. Follow-up, which ranged from 0.25 (25) to 24 (26) years, was short in cases where empty sella developed after pituitary surgery and more prolonged in those where no mass-reducing treatment (either surgical or with high-dose steroids) was used (Supplemental Table 1). Pituitary antibodies were measured in 11 of the 27 patients and found positive in three (11%). Although variable and limited in number, these human data suggest that hypophysitis can be a cause of secondary empty sella and are supported by the present experimental study.

For primary empty sella, the issue of a possible association with hypophysitis and pituitary autoimmunity is more controversial. The clinical setting here is that of a patient diagnosed with empty sella without demonstrable causes (including hypophysitis) who is found to be positive for pituitary antibodies. Considering that hypophysitis can be asymptomatic and undetectable for years, some authors have wondered whether the presence of pituitary antibodies in these patients actually reflect a subclinical form of hypophysitis that has then evolved toward pituitary atrophy and empty sella. The published studies have been difficult to interpret and compare, largely due to the enormous variability in the methods used to detect pituitary antibodies. Komatsu et al. (27) first analyzed 32 patients with primary empty sella for the presence of pituitary antibodies measured by immunofluorescence using mouse corticotroph cells as the antigenic substrate and found them in 24 (75%), significantly more than what was found in normal subjects (zero of 25, 0%). Mau et al. (28) studied six patients with primary empty sella and measured pituitary antibodies by immunoblotting using human GH and ACTH as antigens, reporting two positive (33%), whereas none of the six healthy controls were. Keda et al. (29) studied 48 patients with primary empty sella and measured pituitary antibodies by ELISA using as the antigenic substrate surgically removed human prolactinomas and somatotropinomas, then trypsinized to obtain a suspension of single cells that were then immobilized to the ELISA plates and fixed with glutaraldehyde. Antibodies were found in 25 patients (52%), a significantly higher prevalence than that found in normal adults (three of 65, 5%). Bensing et al. (30) analyzed 30 patients with primary empty sella measuring pituitary antibodies by immunoblotting using 49-kDa α-enolase as the antigen. Antibodies were found in six of the 30 patients (20%), a prevalence not different from that found in healthy controls (11 of 50, 22%). Finally, we reported recently 85 patients with primary empty sella where pituitary antibodies were measured by immunofluorescence using monkey pituitary as substrate. Antibodies were found in five of the 85 empty sella patients (6%), a prevalence significantly higher than that seen in healthy controls (one of 214, 0.5%, P = 0.008 by χ² test) (31). Interestingly, the antibody-positive patients were also hypopituitaric, suggesting that hypopituitarism in empty sella may be the consequence of tissue damage due to hypophysitis.
The variability and lack of standardization in the methods used to detect pituitary antibodies make these five studies difficult to compare. In addition, it is important to consider the timing of antibody measurement. We have shown in this study that pituitary antibodies decrease in titer with decreasing pituitary volume, approaching the upper limit of normality in mice that have an atrophic pituitary. In addition, it is known that antibodies to thyroid antigens progressively disappear after complete ablation of the thyroid (either by surgery or radioiodine), indicating that continued antibody production requires persistence of the targeted antigens (21). Therefore, if primary empty sella is indeed caused by subclinical autoimmune hypophysitis, by the time the empty sella is discovered, the pituitary gland is by definition atrophic and thus predicted to have low antigenic load and consequently low pituitary antibody titers.

Another interesting aspect of this study was the comparison of the MRI findings between mouse and human hypophysitis. In patients, hypophysitis at presentation is radiologically characterized by symmetric enlargement of the pituitary, intense and homogeneous enhancement after gadolinium administration, loss of posterior pituitary bright spot, and thickened pituitary stalk (3). Enlargement and enhancement were mimicked by our mouse model, which also showed that gadolinium enhancement is useful only during the early phase of hypophysitis. This enhancement reflects a hypervascularity of the pituitary that is present early in the disease course but is then replaced by fibrosis in more advanced stages, contributing to both the delayed and reduced enhancement seen in our study. Delayed enhancement has been described in adults with hypophysitis (32) and in children with hypopituitarism (33). Loss of posterior bright spot and thickened stalk, on the contrary, were not seen in murine hypophysitis, in keeping with the observation that this experimental model induces only adenohypophysitis and not infundibulo-neurohypophysitis (4).

In summary, we report the first MRI study of hypophysitis in mice and show that pituitary atrophy and secondary empty sella is the final outcome of autoimmune hypophysitis.

Acknowledgments

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Disclosure Summary: The authors have nothing to disclose.

References


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