Mini-Review

Hypophysitis, the Growing Spectrum of a Rare Pituitary Disease

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Abstract

Hypophysitis is defined as inflammation of the pituitary gland that is primary or secondary to a local or systemic process. Differential diagnosis is broad (including primary tumors, metastases, and lympho-proliferative diseases) and multifaceted. Patients with hypophysitis typically present with headaches, some degree of anterior and/or posterior pituitary dysfunction, and enlargement of pituitary gland and/or stalk, as determined by imaging. Most hypophysitis causes are autoimmune, but other etiologies include inflammation secondary to sellar tumors or cysts, systemic diseases, and infection or drug-induced causes. Novel pathologies such as immunoglobulin G4-related hypophysitis, immunotherapy-induced hypophysitis, and paraneoplastic pituitary-directed autoimmunity are also included in a growing spectrum of this rare pituitary disease. Typical magnetic resonance imaging reveals stalk thickening and homogenous enlargement of the pituitary gland; however, imaging is not always specific. Diagnosis can be challenging, and ultimately, only a pituitary biopsy can confirm hypophysitis type and rule out other etiologies. A presumptive diagnosis can be made often without biopsy. Detailed history and clinical examination are essential, notably for signs of underlying etiology with systemic manifestations. Hormone replacement and, in selected cases, careful observation is advised with imaging follow-up. High-dose glucocorticoids are initiated mainly to help reduce mass effect. A response may be observed in all auto-immune etiologies, as well as in lymphoproliferative diseases, and, as such, should not be used for differential diagnosis. Surgery may be necessary in some cases to relieve mass effect and allow a definite diagnosis. Immunosuppressive therapy and radiation are sometimes also necessary in resistant cases.
Hypophysitis is a rare inflammatory disorder that affects the pituitary gland and infundibulum as a result of an autoimmune, infiltrative, infectious, neoplastic, or sometimes unknown pathogenic processes. Over the past decade, substantial diagnostic advances and increased hypophysitis knowledge and characterization have occurred. Novel etiologies, such as immunoglobulin G4 (IgG4)-related disease, immunotherapy-induced hypophysitis, and paraneoplastic pituitary-directed autoimmunity, have added to a growing hypophysitis disease spectrum. True hypophysitis incidence per year is unknown. Previously reported estimates are 1/9 million individuals (1). Recognition of novel causes, increased use and sophistication of imaging, and increased number of pathology samples postpituitary surgery have led to a hypophysitis disease incidence increase (2,3).

Clinical diagnosis can be challenging since many pituitary lesions, including common pituitary adenomas and rare pituitary metastases, may clinically present with similar characteristics. Diagnosis is based on clinical presentation in conjunction with magnetic resonance imaging (MRI) and laboratory findings, as well as biopsy results in some cases. In this minireview, we discuss the current approach to diagnosis and management of hypophysitis and address common clinical questions.

A PubMed online database search for all study types published in the English language using the terms “hypophysitis,” “pituitary stalk lesions,” “IgG4-related disease,” “immunotherapy, immune checkpoint inhibitors,” “neurosarcoidosis,” “Langerhans cell histiocytosis, LCH,” and “pituitary auto-immunity” was performed in June 2021. Articles were screened by title and abstract and restricted to adults. References from selected articles were also reviewed; articles published within the last 5 to 10 years were preferentially reviewed.

**Hypophysitis: Classification and Pathogenesis**

Hypophysitis is an umbrella term that covers a broad range of inflammatory disorders that affect the pituitary gland. Inflammation can affect only the anterior pituitary (adenohypophysitis), infundibulum and posterior pituitary (infundibulo-neurohypophysitis), or the entire pituitary (panhypophysitis) (1,4). Sometimes this process can extend into the hypothalamus (5) or present as isolated hypothalamic hypophysitis (6,7).

Etiologically, hypophysitis is characterized as primary or secondary. Primary hypophysitis is an isolated condition and includes autoimmune (eg, lymphocytic hypophysitis (LHy)) and other inflammatory or infiltrative forms of isolated pituitary involvement of unknown causes. Secondary hypophysitis develops as a reaction to a local process (eg, rupture of Rathke’s cleft cyst), systemic disease, infection, and neoplastic processes or drugs (8) (Table 1).

Histological classification includes lymphocytic, granulomatous, xanthomatous (9), IgG-4 related, necrotizing hypophysitis, and mixed forms (lymphogranulomatous, xanthogranulomatous) (4,10); LHy is overall the most common form (11,12). Accurate classification is sometimes not possible due to pathological features overlap (4,10,13-23) (Fig. 1).

**Case 1**

A 73-year-old female with a history of ulcerative colitis (in remission) presents with hyponatremia, weakness, and presyncopal episodes over the past year. She notes decreased vision in her right eye. Laboratory evaluations reveal anterior hypopituitarism without diabetes insipidus (DI). Hyponatremia was present and corrected with hydrocortisone and levothyroxine replacement. A pituitary MRI reveals an enlarged and heterogeneously enhancing pituitary gland, with mild mass effect on the optic chiasm and a slightly thickened pituitary stalk (Fig. 2).

**How Does Hypophysitis Typically Present?**

Classically, hypophysitis presents with symptoms related to pituitary deficiencies with or without headaches and vision changes related to the mass effect of an enlarged pituitary gland and infundibulum. Approximately half of patients with primary hypophysitis present with headaches, while 10% to 30% present with visual disturbances related to mass effect (Table 2) (12,24-40).

Symptoms related to loss of anterior and/or posterior pituitary hormones depend on etiology and extent of pituitary damage. Generally, the presence of both anterior pituitary dysfunction and DI is a clue to an inflammatory/infiltrative process, craniopharyngiomas, or metastasis and is highly unlikely in pituitary adenomas. In LHy and immunotherapy-induced hypophysitis, inflammatory process predominantly affects corticotrophs, followed by gonadotrophs and thyrotrophs (24). Importantly, this pattern is distinct from that of pituitary adenomas, where corticotrophs are usually affected last (4,41).
| Etiology                                         | Key clinical features                                      | Laboratory investigation(s) to reach a diagnosis                      |
|-------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------|
| Drug-induced hypophysitis                       | Active or recent use of drug within the last 2 years       | Clinical diagnosis in the context of current/recent immunotherapy    |
| Immune checkpoint inhibitors                    |                                                           |                                                                      |
| Interferon alpha                                |                                                           |                                                                      |
| Ustekinumab                                    |                                                           |                                                                      |
| Daclizumab                                     |                                                           |                                                                      |
| Autoimmune conditions                          | Variable                                                  |                                                                      |
| Thyroid disease                                | Multisystemic involvement                                 |                                                                      |
| Type 1 diabetes mellitus                       | Vitiligo, alopecia                                         |                                                                      |
| Polyglandular syndrome                         | Atrophic gastritis                                         |                                                                      |
| Primary biliary cirrhosis                       | Gonadal failure                                           |                                                                      |
| Autoimmune conditions                          | Multisystemic involvement                                 |                                                                      |
| Connective tissue diseases                     | Multisystemic involvement                                 |                                                                      |
| Sjogren’s                                       | Arthralgias and synovitis                                  |                                                                      |
| Systemic lupus erythematosus                    | Xerostomia and xerophtalmia                               |                                                                      |
| Other                                           | Rash, photosensitivity                                    |                                                                      |
| Inflammatory bowel disease                     | Extrainestinal (arthritis, eye, skin, hepatobiliary and others) | Erythrocyte sedimentation rate, C-reactive protein, Endoscopy        |
| Sarcoidosis                                     | Multisystemic disease causing                             |                                                                      |
| Langerhans cell histiocytosis                   | Rash, lid xanthelasmas or xanthomas                       |                                                                      |
| Erdheim-Chester disease                         | Bone lesions (skull, pelvis, femur)                       |                                                                      |
| IgG4-related disease                            | Pituitary-isolated 4%-5%                                   | Elevated IgG4 levels                                                |
| Vasculitis                                      | Multisystemic disease causing                             |                                                                      |
| Temporal arteritis                              | Arthritis                                                 |                                                                      |
| Granulomatosis with polyangiitis (formerly Wegener) | Headaches, visual symptoms                               |                                                                      |
| Other                                           | Eyes, Skin, Lung, Kidney                                  |                                                                      |
|                                                  | Nervous system                                             |                                                                      |
### Infections

- **Tuberculosis**
  - Very rare, in immunosuppressed patients
  - Leukocytosis or leucopenia
  - PPD skin test or QuantiFERON-TB gold
  - HIV serology
  - Pituitary biopsy: special stains to identify microorganisms
  - PCR for mycobacterium on CSF

- **Syphilis**
- **Bacterial, fungal, viral**

### Paraneoplastic syndromes

- **Anti-Pit-1**
- **Anti-ACTH/POMC**

### Differential diagnosis

| Etiology                          | Key clinical features                             | Laboratory investigation(s) to reach a diagnosis |
|----------------------------------|---------------------------------------------------|--------------------------------------------------|
| **Sellar/para-sellar tumors**    |                                                   |                                                  |
| Craniopharyngiomas               |                                                   |                                                  |
| Germinomas                       | Young males affected                              | Serum AFP and beta-hCG (can be normal in pure cell germinomas) |
|                                    | Frequent DI                                       | CSF, AFP and beta-hCG                            |
| Astrocytomas                      | Craniopharyngiomas                               | Brain imaging                                    |
| Meningioma                        | Intra or supra-sellar cystic lesion               | Biopsy/surgery                                   |
| Other (these can also be secondary causes of hypophysitis) | Bimodal age distribution < 20 and 50–70 years |                                                  |
|                                    | Frequent DI                                       |                                                  |
|                                    | Meningioma                                        |                                                  |
|                                    | Parasellar mass with dural tail                   | Transient upon resolution of the underlying cause |
| **Physiological pituitary hypertrophy** | Homogeneous gland enlargement |                                                  |
|                                    | Usually absent headache                           |                                                  |
|                                    | No panhypopituitarism                             |                                                  |
|                                    | Underlying cause                                 |                                                  |
|                                    | Severe primary gland insufficiency                |                                                  |
|                                    | (gonadotroph hyperplasia of menopause, thyrotroph hyperplasia in severe untreated primary hypothyroidism) |                                                  |
|                                    | Somatotroph hyperplasia of adolescence            |                                                  |
|                                    | Lactotroph hyperplasia of pregnancy              |                                                  |
| **Metastases most frequently from** | Sellar mass with or without suprasellar extension; rarely pituitary stalk thickening only | FDG-PET                                           |
| Lung                              |                                                   | Tissue biopsy                                    |
| Breast                            |                                                   |                                                  |
| Prostate                          | Headaches, vision changes, CN palsy              |                                                  |
| Kidney                            | Anterior hypopituitarism and DI (very frequent)  |                                                  |
| **Pituitary apoplexy**            | Acute or subacute symptoms of headache           | Brain CT: acute hemorrhagic infarct               |
|                                   | Visual deficits/ocular paresis                    | Pituitary MRI: lesion characteristics vary        |
|                                   | Panhypopituitarism without DI                    | Acute: T1 iso- or hyperintense                   |
|                                   | Possible altered mental status                    | Subacute: T1 and T2 hyperintense                 |
|                                   | Anticoagulation is a risk factor                  | Chronic: T1 and T2 hypointense                   |
| **Lymphoproliferative malignancy** | Pituitary may be the sole presenting feature     | Gadolinium: peripheral rim of enhancement         |
| Plasmacytoma                      |                                                   | CBC                                              |
| Lymphoma                          | Cranial nerves frequently affected                | LDH                                              |
|                                   | Frequent DI                                       | Beta2-microglobulin                              |
|                                   | In association with multiple myeloma: anemia, bone pain, renal disease, hypercalcemia | FDG-PET                                           |
|                                   | Extra-pituitary sites of primary pituitary lymphoma: bone marrow, liver, lung, adrenal gland, retroperitoneal lymph node | Serum or CSF flow cytometry                      |
|                                    |                                                   | Oligoclonal bands                                |
|                                    |                                                   | Tissue/bone marrow biopsy                        |
|                                    |                                                   | CSF cytology                                     |
All patients require initial pituitary function testing: 8 AM cortisol [and/or adrenocorticotropin (ACTH) stimulation test]; thyroid-stimulating hormone (TSH); free thyroxine; prolactin; luteinizing hormone (LH); follicle-stimulating hormone (FSH) with estradiol in premenopausal women or testosterone in men; insulin-like growth factor 1 (IGF-1); and serum sodium, plasma, and urine osmolarity if DI is suspected (4,42). Hyponatremia may be observed in adrenal insufficiency (AI), severe hypothyroidism, and syndrome of inappropriate secretion of antidiuretic hormone, and hypernatremia may be observed in uncompensated DI cases. Depending on etiology and clinical context, each unique hypophysitis type may have specific systemic features related to the underlying cause (Table 1).

**What Are the Radiological Features of Hypophysitis?**

Hypophysitis harbors various imaging characteristics. The most frequent MRI finding is a thickened, nondeviated stalk, which can be isolated (infundibuloneurohypophysitis) in one third of patients or associated with mild to moderate symmetric gland enlargement in >80% of patients (39,43). Contrast uptake is usually intense, homogeneous, and less frequently heterogeneous (43). An enlarged pituitary resembles a pituitary macroadenoma in approximately half of patients with primary hypophysitis (24,30,44). While the sellar floor may be eroded in pituitary adenomas, it is usually intact in hypophysitis (45). Other signs of hypophysitis include loss of posterior pituitary bright spot, caused by depletion in vasopressin granules in posterior pituitary hypophysitis (39,46). Dural inflammation may cause a dural tail sign, similar to that observed in patients with a meningioma (10). In late disease stages, the pituitary gland may appear atrophic, and MRI may show sellar arachnoidocele or an empty sella (47,48). Although there are no definite MRI features that can confirm hypophysitis, imaging can be diagnostic in the right clinical context; for example, stalk thickening in a young woman with recent pregnancy presenting with headache and hypopituitarism is highly suggestive of LHy (49). Specific radiologic findings in different types of hypophysitis are presented in Figure 1.

**Case 1 Continued**

The patient undergoes pituitary surgery for this mass with optic chiasm compression. Pathology reveals necrotizing granulomas with giant cells and rich lymphoplasmacytic infiltrate. Staining for microorganisms (Steiner for acid-fast bacilli and fungi; Grocott methenamine-silver nitrate for *Pneumocystis jirovecii*) are negative. There is no evidence of sarcoidosis; angiotensin-converting enzyme (ACE) level is normal; and antineutrophil cytoplasmic antibodies, antinuclear antibody, and thyroid peroxidase antibody are negative.

**Is a Biopsy Always Necessary to Confirm a Hypophysitis Diagnosis?**

Biopsy establishes hypophysitis histopathological type and rules out other etiologies such as neoplasm. However, this is an invasive procedure, and risks and benefits must be carefully weighed. Biopsy is usually considered either when a diagnosis is unclear after initial investigations or when pathology results are needed for treatment (eg, long-term glucocorticoids, immunosuppression, or chemotherapy) (33). There are no established criteria for pituitary biopsy in adults. In the pediatric population, a recent UK consensus proposes biopsy in cases of unclear diagnosis after extensive laboratory, imaging, and cerebrospinal fluid (CSF) investigations, when stalk thickening is ≥6.5mm or when there is clinical deterioration, defined as worsening of hormonal dysfunction, structural disease, or visual disturbances (50). If a biopsy is contemplated, it should be performed by an experienced neurosurgeon in a specialized center (51).
Figure 1. Summary of hypophysitis types, features and treatment options (created with BioRender.com). Histopathology image sources: lymphocytic (author’s [MF] pathology department), granulomatous (17), xanthomatous (9), necrotizing (23), immunoglobulin G4-related (14), and immunotherapy-induced (96). Abbreviations: ACTH, adrenocorticotropic hormone; AI, adrenal insufficienty; APS, autoimmune polyglandular syndrome; DI, diabetes insipidus; DM, diabetes mellitus; ECD, Erdheim-Chester disease; F, female; GC, glucocorticoids; GH, growth hormone; GPA, granulomatosis with polyangiitis; HPF, high power field; LCH, Langerhans cell histiocytosis; M, male; MRI, magnetic resonance imaging; NETs, neuroendocrine tumors; POMC, proopiomelanocortin; PRL, prolactin.
Table 2. Summary of primary hypophysitis studies

| Author, year | Patient demographics | Patient MRI findings | Patient clinical symptoms | Patient pituitary dysfunction | Outcome of patients managed medically<sup>a</sup> |
|--------------|----------------------|----------------------|---------------------------|------------------------------|----------------------------------|
| Angelousi et al (30) | 22 Female, 77% | 45% sellar mass, 36% with autoimmune disease | 59% headache, 32% diplopia | 36% HyperPRL, 32% LH-FSH | Surveillance management (5/22), Glucocorticoid management (8/22), Prednisone 40-60 mg, Improvement: 5% hormonal, 75% hormonal at 5 years, 37% radiological |
| Amereller et al (24) | 60 Female, 73% | 56% stalk thickening, 42% with autoimmune disease | 38% headache, 17% visual impairment | 67% ACTH, 57% TSH | Surveillance management (41/60), Glucocorticoid management (12/60), GC 30 mg-2 g pulse, Improvement: 12% hormonal, 17% hormonal, 25% radiological |
| Atkins et al (35) | 11 Female, 91% | 73% stalk thickening, 55% sellar mass, 36% diffuse enlargement | 55% headache | 36% ACTH, 36% TSH, 27% HyperPRL | Surveillance management (6/11), Glucocorticoid management (1/21), GC dose unknown, Improvement: 0% hormonal, 100% radiological |
| Chiloiro et al (36) | 21 Female, 81% | 57% stalk thickening, 81% with autoimmune disease | 24% headache, 19% visual impairment | 48% DI, 43% LH-FSH, 43% HyperPRL | Surveillance management (4/21), Glucocorticoid management (2/121), GC dose unknown, Improvement: 86% hormonal, 62% radiological, 29% recurrence |
| Honegger et al (26) | 79 Female, 71% | 86% stalk thickening, 50% sellar mass, 22% visual impairment | 62% LH-FSH, 54% DI | 22/79 | Surveillance management (2/29), Glucocorticoid management (7/29), GC 20-500 mg, Improvement: 14% hormonal, 57% radiological, 38% recurrence |
| Imber et al (33) | 21 Female, 62% | 68% diffuse enlargement, 63% stalk thickening | 71% LH-FSH, 57% ACTH | 15/21 (4 GC, 11 surveillance), Improvement: 27% hormonal | Surveillance management (15/21), Glucocorticoid management (7/22), Improvement: 27% hormonal, 47% radiological |
| Imga et al (12) | 12 Female, 75% | 58% stalk thickening, 33% diffuse enlargement | 75% TSH, 52% DI | 4/12 | Glucocorticoid management (4/2), GC 1g pulse + surgery, Improvement: 25% hormonal, 100% radiological |
| Author, year | Patient demographics | Patient MRI findings | Patient clinical symptoms | Patient pituitary dysfunction | Outcome of patients managed medically^a |
|-------------|---------------------|----------------------|--------------------------|----------------------------|---------------------------------------|
|             | n                  | Mean age, years      |                          |                           | Surveillance management | Glucocorticoid management |
| Khare et al (32) | 24   | 32  | 92% diffuse enlargement | 83% headache       | 75% ACTH | 15/24 | Improvement: 33% hormonal | 4/24 | GC 1g pulse | |
|             |       |     | 88% stalk thickening    | 13% diplopia         | 58% TSH  |     | 100% radiological |               |               | |
| Korkmaz et al (39) | 17   | 31  | 47% sellar mass         | 53% headache        | 59% ACTH | 10/17 | Improvement: 10% hormonal | 5/17 | GC 120mg, rescue | |
|             |       |     | 41% stalk thickening    | 12% visual impairment| 53% TSH  |     | 30% radiological |               |               | |
|             |       |     | 6% with autoimmune disease |            | 47% LH-FSH |     |                   |               |               | |
|             |       |     | 18% diffuse enlargement |                          | 41% DI   |     |                   |               |               | |
| Krishnappa et al (40) | 39   | 39  | 85% diffuse enlargement |                          | 64% ACTH | 21/39 | Improvement: 43% hormonal | 18/39 | GC 1g pulse | |
|             |       |     |                           |                          | 56% TSH  |     | 48% radiological |               |               | |
|             |       |     |                           |                          | 54% LH-FSH|     |                   |               |               | |
|             |       |     |                           |                          | 18% DI   |     |                   |               |               | |
|             |       |     |                           |                          | 41% HyperPRL|    |                   |               |               | |
| Kyriacou et al (38) | 22   | 38  | 64% sellar mass          | 68% headache        | 86% ACTH | 13/22 | Improvement: 0% hormonal | 3/22 | Postoperative, GC dose unknown | |
|             |       |     | 32% visual impairment    |                          | 59% TSH  |     |                   |               |               | |
|             |       |     |                           |                          | 41% LH-FSH |     |                   |               |               | |
|             |       |     |                           |                          | 32% DI   |     |                   |               |               | |
|             |       |     |                           |                          | 23% HyperPRL|    |                   |               |               | |
| Lupi et al (34) | 12   | 47  | 66% stalk thickening     | 33% headache        | 83% DI   | 4/12  | Improvement: 50% hormonal | 8/12 | GC 40 mg | |
|             |       |     | 33% diffuse enlargement  |                          | 50% LH-FSH |     | 100% radiological |               |               | |
|             |       |     |                           |                          | 42% TSH  |     |                   |               |               | |
|             |       |     |                           |                          | 33% ACTH |     |                   |               |               | |
| Park et al (31) | 22   | 47  | 77% stalk thickening     | 27% headache        | 82% DI   | 12/22 | Improvement: 36% hormonal | 7/22 | GC 50-500 mg | |
|             |       |     | 59% diffuse enlargement  | 9% visual impairment | 36% ACTH |     | 17% radiological |               |               | |
|             |       |     |                           |                          | 36% TSH  |     |                   |               |               | |
|             |       |     |                           |                          | 32% LH-FSH|     |                   |               |               | |
|             |       |     |                           |                          | 23% HyperPRL|    |                   |               |               | |
| Oguz et al (27) | 20   | 41.5| 24% diffuse enlargement  | 63% headache        | 66% LH-FSH | 1/20 | surveillance |               |               | |
|             |       |     | 18% stalk thickening     | 37% visual impairment | 61% TSH  |     |                   |               |               | |
|             |       |     |                           |                          | 39% ACTH |     |                   |               |               | |
|             |       |     |                           |                          | 32% HyperPRL|    |                   |               |               | |
|             |       |     |                           |                          | 28% DI   |     |                   |               |               | |
Overall, there 5 hypophysitis histological subtypes described in Figure 1 (4,13-23).

Case 2

A 71-year-old male presents with headaches, anterior hypopituitarism, and DI. Pituitary MRI shows heterogeneous suprasellar stalk lesion with cystic change of approximately 1 cm (Fig. 3), and biopsy reveals polyclonal lymphocytic infiltration (CD3+ T cells and CD20+ B cells) with CD68+ macrophages, leading to a presumed LHy diagnosis. The patient declines high-dose glucocorticoid (GC) treatment and is lost to follow-up. Over the following 3 years, headaches worsen, and the lesion has enlarged to 2 cm. The patient undergoes pituitary surgery. Pathology reveals a papillary craniopharyngioma; WHO grade I, with extensive reactive xanthogranulomatous changes including abundant macrophages and numerous giant cells and cholesterol clefts. The patient continues to be panhypopituitary; headaches have completely resolved. There is no evidence of residual disease at last postoperative follow-up (3 years).

This rare case demonstrates a spectrum of inflammatory pituitary changes that can occur secondary to other sellar tumors and highlights the need for repeat imaging and further workup if clinical course is atypical for presumed LHy.

What Other Workup Can Be Performed to Elucidate a Hypophysitis Diagnosis and Differential Diagnosis?

Pituitary biopsy may be the only modality that allows for a definitive diagnosis. However, a minority of patients will undergo a surgical procedure, as careful clinical evaluation may orient toward a probable diagnosis (52).

Demographic information is important to guide investigations. For instance, stalk thickening in a young female is suggestive of LHy, while in a child or adolescent, it should prompt investigations for germinoma; in older aged adults, other malignancies such as lymphoma should be considered (52).

A baseline workup includes a complete blood count, sedimentation rate, C-reactive protein, calcium, creatinine, urinalysis, and ALT. Specific investigation are further tailored to clinical features: IgG4, ACE, antineutrophil cytoplasmic antibodies, antinuclear antibody, lactate dehydrogenase, B2-microglobulin, alpha-fetoprotein, human chorionic gonadotropin, tuberculin skin test, or QuantiFERON-TB Gold. Key clinical features of systemic disease associated with hypophysitis and laboratory investigations to be considered are listed in Table 1. Serum antipituitary antibodies may be present; however, they lack specificity as they are...
commonly present in patients with different autoimmune disorders without pituitary involvement as well as in pituitary adenomas (53-55). Therefore, their measurement is of little clinical use currently. Recently, pituitary-specific positive transcription factor 1 (Pit-1) has been described as an antigen target in LHy, but antibody assays are not widely available (56).

Whole-body computed tomography or fluorodeoxyglucose-positron emission tomography (FDG-PET) could determine other affected sites in systemic diseases including sarcoidosis, tuberculosis (TB), granulomatosis with polyangiitis, malignancy, and IgG4-related disease, including other accessible locations for potential tissue biopsy; FDG-PET may reveal multisystemic hyperfunctional lesions (31,57). Whole-body imaging is recommended in patients with isolated stalk lesions and no LHy clinical context or when malignancy or infiltrative disease is highly suspected.

CSF analysis for cytology, flow cytometry, immunochemistry (including ACE, human chorionic gonadotropin, and alpha-fetoprotein) and culture can be also helpful if initial investigations are negative and neoplastic process or infection are suspected (25,52), as well as in evolving disease determined by either progressive hormonal dysfunction, increasing size of pituitary/stalk lesion, and/or visual deterioration (50).

If all these investigations are negative, a trial of empiric high-dose GC could be considered as most of the infiltrative and inflammatory conditions will have similar treatment (high-dose GC and/or immunosuppression). However, biopsy should be reconsidered in patients with unfavorable clinical course as biopsy-confirmed diagnosis would allow...
the selection of appropriate therapy and avoid delays in treatment of other diseases, especially hematologic or solid malignancies.

Case 3
A 30-year-old female presents with polydipsia and polyuria, and laboratory findings are consistent with DI. The patient is otherwise healthy, with a history of lichen sclerosus. Pituitary MRI reveals 5-mm stalk enlargement (Fig. 4). Anterior pituitary function is intact. The patient is treated with desmopressin and observed with serial MRIs, which show stability over a period of 3 years. The patient experiences an uneventful spontaneous pregnancy and delivery; pituitary MRI 2 years after delivery shows regression of thickened stalk. A near complete resolution of the stalk thickening is observed on MRI 12 years after delivery. Diabetes insipidus persists, and the patient continues to take desmopressin. This patient has never had a pituitary biopsy or treatment with high-dose GC, but probable diagnosis is LHy.

How Should Hypophysitis Be Treated?
Treatment should be geared toward the underlying disease etiology and severity.

GCs have been considered the mainstay of treatment for primary hypophysitis as GCs target the inflammatory process; however, spontaneous resolution of pituitary infiltration with/without permanent pituitary dysfunction can occur frequently. In a German cohort, 46% of patients with primary hypophysitis managed by observation only showed radiological improvement, and one third had hormonal recovery, mainly vasopressin and ACTH (37). In the chronic phase, when irreversible changes have occurred, anti-inflammatory treatment may not affect radiologic or hormonal outcome (58).

As no randomized controlled studies have been performed, it is unclear whether GC allows for better pituitary function recovery vs simple observation. Given a broad spectrum of GC side effects, risks and benefits should be weighed when deciding whether to treat mild cases of primary hypophysitis.

Clinical signs and symptoms should guide a decision to manage patients solely by observation. In patients with mild to moderate headache, mild pituitary dysfunction, no mass effect on optic chiasm, and probable LHy, observation may be safely considered (24,37). Initial clinical surveillance can be performed with pituitary MRI at 3 to 6 months. This imaging interval can be prolonged if disease evolution is favorable. However, if lesions are causing a significant mass effect at baseline or follow-up, either GC treatment, biopsy, or both should be performed (6). During observation, periodic re-evaluation for pituitary function recovery is needed. Additionally, clinicians should be alert for new symptoms affecting other organs as systemic disorders such as sarcoidosis, Langerhans cell histiocytosis (LCH), and IgG4-related disease may manifest later in the course of disease (59,60).

Primary hypophysitis has very variable GC response rate, from 20% to >95% in a partial or complete hormonal and radiographic response (12,24-40). Overall improvement in endocrine function occurs less than reduction in pituitary mass, which can attain closer to a 75% response rate (11,12,24-40) (Table 2). Earlier GC initiation has been shown to improve hormonal recovery (40). Interestingly, some retrospective studies have revealed better pituitary function outcomes with observation vs GC administration; however, milder and potentially reversible cases were probably less likely to be treated with GC (24,35,37).

Figure 4. Case 3—Lymphocytic hypophysitis with isolated infundibulo-neurohypophysitis. Postcontrast T1 pituitary magnetic resonance imaging sagittal; left, baseline, stalk thickening measuring 5 mm in diameter, otherwise normal-size pituitary gland; middle, 5 years after initial presentation, spontaneous regression of stalk thickening, now approximately 2 mm in diameter; and right, 12 years after initial presentation, complete resolution of stalk thickening.
Studies prednisone doses for treatment of primary hypophysitis range widely, between 20 mg/day initial dose to 1 g methylprednisolone pulse therapy. Due to the rarity of this condition and a lack of large randomized prospective clinical trials, the exact dose, duration, and even indication for GC is still a matter of debate. Some authors advocate use of pulse regimens of high-dose methylprednisolone (120 mg-1 g) intravenously (40,61). In a series of 39 patients, intravenous pulse followed by high-dose prednisone resulted in a 2-fold hormonal recovery rate compared to patients with observation (86% vs 43%, \( P = 0.0007 \)) (40). Lower GC doses may also be effective. A prospective study compared 12 patients treated by 50 mg prednisone for 3 months with a slow taper to 8 patients managed by observation. At the end of a 2-year follow-up, more prednisone-treated patients (58.3%) compared to untreated patients (25%) improved their pituitary function, and 66% of treated vs 25% of untreated had radiographic improvement (46).

Studies comparing pulse or higher-dose vs lower-dose GC regimen are lacking. A 1 mg/kg/day dosing with slow taper may be preferred to GC pulse therapy to reduce risk of recurrence (34,46). However, recurrence can develop even during the steroid taper (37). In a series of 76 patients with primary hypophysitis, almost half (32/76) received GC treatment at some stage with a good initial response in almost all cases, but relapse and treatment failure occurred in 40% (37). No correlation was observed between duration of therapy and initial dose.

Immunosuppression with rituximab, azathioprine, or methotrexate may be considered in GC-refractory cases and as GC-sparing options. Azathioprine is the most studied and appears superior for mass reduction than hormonal improvement (10,11). Similar results have been observed with methotrexate and mycophenolate mofetil (10). Rituximab, an anti-CD20+, can be used in B-lymphocytes predominant diseases and relapsing IgG4-related disease (62,63); complete remission is possible (64,65).

Surgery may be used not only for decompression of optic chiasm and GC-resistant cases but also to confirm diagnosis in cases where diagnosis needs clarification. In a large series of 60 patients with primary hypophysitis, patients who underwent surgery had a worse outcome, based on symptoms and endocrine dysfunction (24). However, it is likely that patients who had surgery had more severe baseline disease.

Fractionated radiotherapy and stereotactic radiosurgery have been used successfully in a few patients requiring multimodal therapy (10,37). For treatment-resistant and recurrent LHy, radiosurgery is an option to allow mass control and discontinuation of immunosuppression (66,67). Treatment of other specific types of hypophysitis is addressed in the following discussion. A suggested hypophysitis treatment management algorithm is outlined in Figure 5.

### Specific Hypophysitis Types

#### Lymphocytic Hypophysitis

Lymphocytic hypophysitis comprises approximately two thirds of cases of primary hypophysitis forms and occurs more commonly in females (2:4:1 female:male ratio); children and elderly may also be affected (4,25,30). In women, LHy occurs peripartum in more than half, either in late pregnancy or early postpartum with a peak occurrence during the third trimester (58). Interestingly, a few reports have shown a much weaker association of LHy with pregnancy; in one study, 11% of women had a recent pregnancy history, and in another study, 1/21 (5%) (26,32). Association with a personal or familial history of autoimmune disease (such as autoimmune thyroid disease, lupus, primary biliary cirrhosis, celiac disease, among others) is frequent, and specific human leukocyte antigen DQ8 and DR3 alleles are predisposing (41).

Lymphocytic hypophysitis appears to be a T cell-mediated event. In a murine model of hypophysitis, T cells activation rather than autoantibody/B cell infiltration is demonstrated. CD4+ T cells predominate and harbor a specific phenotype with T helper 17 and 1 cells, respectively, producing interleukin 17 and interferon-gamma (68,69).

Treatment of LHy is described in the previous discussion as treatment of primary hypophysitis. In cases of severe headache and significant mass effect, high-dose GCs are first-line treatment. Response to systemic GC treatment is usually good in LHy but notably less than in IgG4-related disease (70). Of note, secondary masslike inflammation due to a local or systemic process might also respond, especially in patients with a central nervous system lymphoma (71); thus, GC response does not confirm a presumptive diagnosis of LHy (40).

#### Granulomatous Hypophysitis

Granulomatous hypophysitis comprises approximately 20% of primary hypophysitis cases; similar to LHy, has a female predominance (2.5:1); and can be associated with autoimmune disorders (4,26). It usually manifests in the fourth decade of life.

Clinical presentation may be indistinguishable from LHy; however, several series have shown more severity, with more frequent headaches, higher rates of anterior hypopituitarism, DI (up to 75%), and degree of radiographic abnormality (26). Moreover, granulomatous hypophysitis is usually less GC-responsive compared to LHy (10,58).
Granulomatous forms of hypophysitis related to systemic disorders may not always manifest with multisystem involvement.

Sarcoidosis is a systemic autoimmune disorder with formation of noncaseating granulomas. Pituitary involvement occurs in <1% of sarcoidosis cases. Sinonasal granulomas may be contiguous with the sella (59). Cranial nerves, as well as basal hypothalamus and the third ventricle floor, may be affected by the process (8,59). Interestingly, hypophysitis may be its only presenting feature. In a series of hypothalamo-pituitary sarcoidosis, only 11/24 (46%) patients had a previous diagnosis of sarcoidosis (59). However, patients with pituitary involvement had higher risk of developing systemic disease, with 71% lung, 58% neurologic, 38% sinus, and 33% with ocular involvement (59). Only one third of patients had an elevated serum ACE vs 71% controls without pituitary involvement (59). Elevated enzyme in CSF is found in approximately 50% of cases (72). Hypogonadism was the most frequent axis affected, and DI was present in half of cases. Sarcoidosis is evoked if a certain percentage of granulomas are found at biopsy (13,59,73). Pituitary MRI changes include a hypothalamic-pituitary or stalk thickening in almost all cases, which regress upon GC treatment. However, hormonal abnormalities persist long term (59).

Granulomatosis with polyangiitis hypophysitis is rare (<1%) and is usually found in association with multisystem disease (ear, nose, and throat disease and lung, as well as kidney, skin, eyes, and arthralgias) (74,75). However, pituitary involvement as an initial presentation was noted in almost half of cases (75). There is a predilection in young females, and DI is almost universally present (74,75). First-line treatment is GCs; other treatment options include immunosuppressive agents such as cyclophosphamide (74,75).

Pituitary tuberculoma, is a rare presentation of TB. Interestingly, primary pituitary involvement can occur without multisystemic involvement. Most cases reported are
in patients originating from endemic regions (76). Typical clinical presentation is an afibrile patient with headaches, visual impairment, and hypopituitarism with DI (76). Histology shows caseating and necrotizing granulomas. Acid-fast bacilli and Ziehl-Neelsen stains are usually negative in pituitary TB, but polymerase chain reaction for mycobacterium on CSF can confirm diagnosis (76,77). In a German series, 3/7 cases of hypophysitis with granulomatous inflammation on biopsy were diagnosed with TB; none were diagnosed with miliary disease (12). Pituitary TB is treated with a combination of antituberculous medications (76).

Histiocytosis

Histiocytosis is a spectrum of disease originating from abnormal Langerhans cells (dendritic or antigen-presenting cells) and includes LCH and Erdheim-Chester disease (ECD). Hypothalamic-pituitary involvement is more frequent in LCH than ECD (78). In both conditions, infiltration preferentially affects neurohypophysis, with DI the most common presenting feature, sometimes even predating the diagnosis. Notably, LCH is most often encountered in children but can also occur during adulthood. Systemic manifestations in LCH and ECD mainly affect dermatological and skeletal systems. In LCH adults, 50% of patients will show lytic bony lesions (with skull, pelvis, and femur most affected), but most are asymptomatic (60,79-82). In ECD, bone involvement usually presents as osteosclerotic painful lesions affecting the lower limbs (80,81). Skin manifestations may present as a rash (LCH) or lid xanthelasmas or xanthomas (ECD). Other system involvement may include cardiovascular, respiratory, polyadenopathy, and hepatosplenomegaly (81,82).

Hypothalamic-pituitary infiltration occurs more commonly in those with systemic involvement. Pituitary biopsy will demonstrate granulomatous involvement of monoclonal Langerhans cells (CD1a+ and CD207+) along with polyclonal inflammatory cells, notably T lymphocytes, macrophages, and eosinophils (79). In ECD, histiocytes are CD68+ and CD1a− (80,81).

DI and growth hormone abnormalities are the most common (15%-50%) followed by hypogonadism (34%), ACTH (15%-21%), and TSH (16%-23%) deficiencies (83). Some may present with hypothalamic dysfunction including hyperphagia, adipisia, impaired thermoregulation, and sleep, memory, and behavioral disturbances (8,83). Treatment modalities include surgery, GCs, immunosuppressive agents, chemotherapy, radiotherapy and targeted agents (BRAF inhibitors, MEK inhibitors) (82).

IgG4-related Hypophysitis

IgG4-related hypophysitis is a plasma cell hypophysitis that may present either as an isolated pituitary lesion (sometimes classified as primary hypophysitis) or a multisystemic disease. It is characterized by a dense infiltration of lymphocytes and IgG4-positive plasmacytes, leading to fibrosis with characteristic cartwheel pattern in the advanced stages. IgG4-related disease may affect a wide range of organs, thus leading to a spectrum of clinical manifestation, the most frequent being retroperitoneal fibrosis, sclerosing sialadenitis, adenopathy, and pancreatitis but may also include lung interstitial inflammation, pericardial and vascular fibrosis, nephritis, or Riedel thyroiditis (84,85).

IgG4 hypophysitis is now increasingly recognized; in 2 reviews comprising 52 idiopathic hypophysitis cases, 30% to 40% were confirmed a posteriori with IgG4-related disease (2,16). Mean age at diagnosis is 55 to 65 years old, males being more frequently affected with multisystemic disease (84-86). Pituitary involvement in IgG4-related disease affects 4% to 5% of patients (87,88) and could be the sole presenting feature in 10% to 30% of those, mostly in women (84-86). The vast majority will thus have multiorgan involvement, and investigations including whole-body imaging is advised (70). FDG-PET scanning may reveal multisystemic hyperfunctional lesions (31,57).

Diagnosis is established based on the previously described histologic criteria or on compatible MRI findings combined with (1) other tissue biopsy proven disease or (2) elevated IgG4 levels >140 mg/dL and a good response to GC treatment (15).

Combined anterior hormone deficiency with DI is observed in 20% to 40% of cases (84-86). In more than half of patients both pituitary and stalk are enlarged on imaging (84). Notably, 15% to 25% of patients will have normal IgG4 serum levels, mostly women (84-86). Response to supraphysiological GC doses is universal and prevents fibrosis (84); prednisone, 30 to 40 mg per day, is usually given for 1 to 2 months and then tapered over 2 to 6 months (70). Relapses are infrequent, and rituximab might be a good alternative in these cases (85,89).

Immunotherapy-related Hypophysitis

Immunotherapy to increase host response to recognize tumor cells revolutionized oncology treatment. These molecules inhibit the self-tolerance and tumoral immune escape allowing T-cell activation, ultimately allowing an enhanced host immunologic response toward cancer cells. The main molecular targets are the cytotoxic T-lymphocyte protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death ligand 1 (PD-L1), the first 2 located on T cells, and the latter on the antigen-presenting and tumor cells. CTLA-4 inhibitors (CTLA-4i; eg, ipilimumab, tremelimumab) act earlier in the immune response while PD-1 and PD-L1 inhibitors (PD-1/PD-L1i; eg, nivolumab and pembrolizumab) act more peripherally at the tumor level (3).
In parallel, immune-related events occur as side effects and can affect multiple organs and system including the pituitary gland. Mechanisms include autoantibodies directed to the pituitary and complement activation (type 2 hypertuitar gland. Mechanisms include autoantibodies directed and can affect multiple organs and system including the pi-

Not all immunotherapy drugs have the same effect on the pituitary gland. A comprehensive cohort analysis on check-

The role of imaging in diagnosis is less clear in these patients and is mostly used to exclude other causes of hypopi-

Risk factors for immunotherapy-induced hypophysitis include male sex, older age, and possibly higher doses of the culprit drug (3). However, there are no specific predictors; clinical assessment and regular adrenal and thy-

Cortisol axis evaluation can be challenging in patients who have received high-dose GCs and/or have dysalbuminemia and/or acute illness (99). An ACTH stimulation test might be falsely normal if the event is acute. As primary AI has also been described (much rarer), obtaining ACTH levels is important (100). Patients should be educated about symp-

Physiologic hormone replacement with hydrocortisone and/or thyroxine is recommended. Delaying immuno-

Paraneoplastic Pituitary Autoimmunity

Recent advances in the understanding of pituitary auto-

Conclusion

In conclusion, in the last few years there has been a rich and innovative expansion of knowledge related to the
pathophysiology of novel types of hypophysitis, including immunotherapy-induced, IgG-4-related disease, and paraneoplastic pituitary autoimmunity. Pituitary inflammation can present either as an isolated autoimmune event or can be secondary to various multisystemic conditions. With increasing incidence of hypophysitis, heightened clinical awareness is advised. While many pituitary lesions may mimic hypophysitis, a thorough history and clinical examination combined with biochemical, pituitary imaging, and, in selected cases, histological findings often allow the establishment of a correct diagnosis. In addition to hormonal replacement, high-dose GCs may be indicated in some patients; while mass effect will likely improve, pituitary function rarely returns to normal. Further studies on the characterization of the various hypophysitis facets will allow for a more accurate diagnosis and individualized patient treatment.

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