Hypophysitis: diagnosis and treatment

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Abstract

Hypophysitis is a rare condition characterised by inflammation of the pituitary gland, usually resulting in
hypopituitarism and pituitary enlargement. Pituitary inflammation can occur as a primary hypophysitis (most
commonly lymphocytic, granulomatous or xanthomatous disease) or as secondary hypophysitis (as a result of systemic
diseases, immunotherapy or alternative sella-based pathologies). Hypophysitis can be classified using anatomical,
histopathological and aetiological criteria. Non-invasive diagnosis of hypophysitis remains elusive, and the use
of currently available serum anti-pituitary antibodies are limited by low sensitivity and specificity. Newer serum
markers such as anti-rabphilin 3A are yet to show consistent diagnostic value and are not yet commercially available.
Traditionally considered a very rare condition, the recent recognition of IgG4-related disease and hypophysitis as a
consequence of use of immune modulatory therapy has resulted in increased understanding of the pathophysiology
of hypophysitis. Modern imaging techniques, histological classification and immune profiling are improving the
accuracy of the diagnosis of the patient with hypophysitis. The objective of this review is to bring readers up-to-
date with current understanding of conditions presenting as hypophysitis, focussing on recent advances and areas
for future development. We describe the presenting features, investigation and diagnostic approach of the patient
with likely hypophysitis, including existing conventional techniques and those in the research/development arena.
Hypophysitis usually results in acute and persistent pituitary hormone deficiency requiring long-term replacement.
Management of hypophysitis includes control of the inflammatory pituitary mass using a variety of treatment
strategies including surgery and medical therapy. Glucocorticoids remain the mainstay of medical treatment but
other immunosuppressive agents (e.g. azathioprine, rituximab) show benefit in some cases, but there is a need for
controlled studies to inform practice.

Invited Author’s profile
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include clinical aspects of pituitary disease and inherited endocrine conditions.
Introduction

Hypophysitis is the collective term for conditions presenting with inflammation of the pituitary gland and infundibulum. Hypophysitis can occur as a primary entity or secondary to a predisposing local sella or multi-systemic inflammatory conditions. Hypophysitis is a rare condition; however, the recent recognition of IgG4-related disease (IgG4-RD) and the introduction of immune checkpoint inhibitors, as cancer therapies with endocrine adverse effects has prompted increased interest in inflammatory disorders affecting the pituitary gland. In the existing literature, the term hypophysitis has been used to describe a number of conditions that present with either primary or secondary inflammation of the pituitary gland. There has been inconsistency in the classification and commonly overlap in using the term for both inflammatory and neoplastic processes (including Langerhan’s cell histiocytosis (LCH)). This highlights the potentially broad differential that must be considered in the patient presenting with clinical and investigative features consistent with hypophysitis. This review guides the reader through the classification systems and highlights the diagnostic strategy. Recently recognised and emerging forms of hypophysitis are discussed in detail.

Hypopituitarism related to infective conditions has been documented for over a century (1), but it is only in the last 50 years that we have been able to begin to evaluate the primary pathologies leading to hypophysitis (2). Histological description of some of the originally described case reports suggests that lymphocytic infiltration of the gland was noted as early as the beginning of the last century (1), and in the 1950s, this was identified to have an autoimmune association (3). Our understanding of hypophysitis has grown considerably in the last decade, with contributions from large case series and comprehensive review articles (4, 5, 6).

The overall prevalence of these diseases remains low and hypophysitis is still considered a rare condition. Population-based studies report an incidence of hypophysitis (all types combined) to be about 1 in 9 million (4), but this is an underestimate, particularly as IgG4-related disease and involvement of the hypophysis by systemic pathologies has increasingly been recognised. Neurosurgical centres report hypophysitis prevalence to be of <1% of sella and suprasella lesions referred for evaluation (0.24–0.88% (4, 7)).

This review summarises the current literature on the diagnosis and management of hypophysitis, with emphasis on discussion of the newer and less common clinical entities such as immune checkpoint therapy-related hypophysitis and IgG4 hypophysitis. Little is known about the optimal diagnostic approach and treatment of both primary and secondary hypophysitis and we have summarised the available literature. We have also included areas of future research and future anticipated clinical developments. The review provides guidance for the clinician investigating and managing patients presenting with hypophysitis.

Data collection

We performed a PubMed-based search of articles using the search terms hypophysitis, adenohypophysitis, infundibulohypophysitis, autoimmune infection, IgG4 granulomatous xanthomatous autoimmune, infection, IgG4, granulomatous, xanthomatous, immune checkpoint, CTLA-4, PD1, PD-L1 and combined them with hypophysitis, hypopituitarism, pituitary. After the original search, we used filters to select articles available in English, articles with available full texts and removed duplicate articles resulting in 1074 articles. Further short-listing was done based on the relevance of the titles using filtering for mesh terms or text-words. The final search derived 271 articles. Of these, 53 articles were review articles, 169 were case reports and 49 were other journal articles.

Classification of hypophysitis

In clinical practice, the term hypophysitis is used as an umbrella encompassing the conditions that present as a result of either primary or secondary pituitary hypophysitis. A number of classification systems have evolved to categorise hypophysitis. These include using aetiology, pattern of pituitary involvement and histological findings. In many patients, histological confirmation of the pathology has not been possible. Therefore, using a solely histology-based classification mechanism has not been possible for all patients. It is conventional to classify based on aetiology (or presumed aetiology); with conditions described as either primary (affecting the hypothalamo-pituitary structures) or secondary hypophysitis. The commonest primary condition is lymphocytic hypophysitis with idiopathic granulomatous hypophysitis being less common. Secondary causes include autoimmune conditions (e.g. systemic lupus erythematosus, autoimmune polyglanular syndrome). Traditionally infiltrative conditions including LCH and...
sarcoidosis have been included in the hypophysitis category. Drug therapy-induced hypophysitis, especially with CTLA-4 inhibitors, is a new entity increasingly recognised by oncologists and endocrinologists.

Historically, hypophysitis has also been just classified according to the pattern of the hypothalamic, pituitary and pituitary stalk (PS) involvement. This approach is limited as it does not necessarily relate to the particular aetiology but does have implications for describing the associated pituitary hormone deficits that arise. Patients with involvement of the neurohypophysis and those with pan-hypophysitis typically present with diabetes insipidus related to ADH deficiency. Those with pure involvement of the anterior pituitary do not have diabetes insipidus but present with the consequences of anterior pituitary hormone deficiency.

Hypophysitis can also be classified using histological appearances. Biopsy is most commonly performed to distinguish between neoplastic and inflammatory conditions and ideally make a categorical diagnosis. When a successful biopsy has been achieved, this approach is useful in guiding management decision making. There is overlap in the presentation of granulomatous, lymphocytic and xanthomatous lesions and making clear distinction between these entities is not always possible. Existing reports are mostly retrospective and are limited by lack of diagnostic histopathology. The classification of primary hypophysitis and secondary predisposing factors are summarised in Tables 1 and 2.

### Clinical presentation of hypophysitis

Pituitary inflammation (either primary or secondary) usually results in pituitary hormone deficiency and enlargement of the pituitary gland. Inflammatory or infiltrative expansion of the pituitary gland can result in compression of the optic apparatus with resulting neuro-ophthalmic consequences. These usually include visual field defects but reduction in colour perception and visual acuity can also occur. Involvement of the cavernous sinus with ophthalmoplegia is rare but described (8). Headache is a consistently reported symptom in the patient with hypophysitis.

Endocrine manifestations include anterior pituitary hormone deficiencies, diabetes insipidus and abnormal serum prolactin (either hypo or hyperprolactinaemia (6). The pattern of endocrine dysfunction maybe influenced by the aetiology. Lymphocytic hypophysitis is considered to have a predilection to ACTH, gonadotrophin, TSH, GH deficiencies in this sequence, but isolated hormone deficiencies though rare, have been reported (4, 9). The pattern of hormone deficits may differ in IgG4-RD and immune checkpoint inhibitor-related hypophysitis. It has been suggested that hyperprolactinemia is a feature predominantly seen in the acute phase of the lymphocytic hypophysitis, and simultaneously, other symptoms of pituitary enlargement may be present (5). Involvement of PS in isolation (infundibulo-hypophysitis) and entire involvement of the pituitary gland and stalk (pan-hypophysitis) are more likely to present with diabetes insipidus (the latter including anterior pituitary hormone deficiency).

Headache with or without nausea, vomiting (>50%) and visual disturbances are common, as described in large case studies (6, 10). Cranial nerve palsies (10, 11), cavernous sinus involvement (10), intracavernous carotid

### Table 1 Classification of primary hypophysitis (adapted and modified from(91)).

<table>
<thead>
<tr>
<th>(a) Based on anatomy</th>
<th>Lymphocytic adenohypophysitis</th>
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<tr>
<td></td>
<td>Lymphocytic infundibuloneurohypophysitis</td>
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<td></td>
<td>Lymphocytic pan-hypophysitis</td>
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<tr>
<td>(b) Based on histology</td>
<td>Lymphocytic hypophysitis</td>
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<td>Granulomatous hypophysitis</td>
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<td></td>
<td>Xanthomatous hypophysitis</td>
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<td></td>
<td>Plasmacytic/IgG4-related hypophysitis</td>
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<td></td>
<td>Necrotising hypophysitis</td>
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<td></td>
<td>Mixed forms (lymphogranulomatous, xanthogranulomatous)</td>
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### Table 2 Conditions predisposing to the development of hypophysitis.

<table>
<thead>
<tr>
<th>Autoimmune conditions</th>
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<tr>
<td>Systemic lupus erythematosus (SLE)</td>
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<tr>
<td>Autoimmune polyglandular syndrome (APS)</td>
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<tr>
<td>Systemic inflammatory disorders</td>
</tr>
<tr>
<td>• Sarcoïdosis</td>
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<tr>
<td>• Granulomatosis with polyangitis</td>
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<tr>
<td>• IgG4-disease</td>
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<tr>
<td>• Other granulomatous (Crohn’s, Takayasu’s, Castleman’s disease)</td>
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<tr>
<td>Drug induced</td>
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<tr>
<td>• Immune checkpoint therapy (CTLA4 Ab, PD-1 Ab)</td>
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<tr>
<td>• Interferon α</td>
</tr>
<tr>
<td>Infiltrative lesions</td>
</tr>
<tr>
<td>• Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>• Erdheim–Chester disease</td>
</tr>
<tr>
<td>Local tumour effect (Sellar diseases)</td>
</tr>
<tr>
<td>• Rupture of Rathke’s cleft cyst</td>
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<tr>
<td>• Germinoma</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>• Tuberculosis</td>
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<td>• Syphilis</td>
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<td>• Fungal infections</td>
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artery occlusion (12), meningitis-mimic (13) and even apoplexy-mimic (11, 14) presentations have been reported. Amongst the other common non-endocrine symptoms reported in a recent German study include weight gain and features of associated autoimmune conditions (10).

The relationship to pregnancy and known existing conditions and their treatments are important to identify the aetiology of hypophysitis. A relationship with pregnancy (particularly third trimester or early post-partum) provides evidence to support a diagnosis of lymphocytic hypophysitis.

Given the possibility that hypophysitis may be secondary to a systemic condition or an infiltrative disorder, it is important to consider a broad history and examination. Conditions such as sarcoidosis or LCH might manifest with symptoms of respiratory or bone disease. Drug history may be relevant, especially when newer oncology medications are used as immune therapy. Immune checkpoint inhibitors, most commonly ipilimumab, result in hypophysitis and thyroiditis as recognised adverse effects. A large case series of 152 PS lesions reported neoplastic lesions (32%) were more common than inflammatory pathologies (20%), highlighting the relevance of a broad differential (15).

**Investigation of the patient with hypophysitis**

1. **Biochemistry**
   2. A full early morning pituitary-related hormonal profile including cortisol, ACTH, IGF-1, GH, oestradiol (pre-menopausal females)/testosterone, LH, FSH, free thyroxine, TSH, prolactin, plasma/urine osmolality, electrolytes should be a part of the hormonal work up. Biochemical evaluation of the gonadotrophin axis may not be indicated in a pre-menopausal female with normal menstruation. In patients with suspected diabetes insipidus, levels of anti-diuretic hormone should be measured, where feasible. Routine baseline investigations such as full blood count, peripheral smear, renal, liver and bone profile, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) can provide subtle clues to the nature of the systemic process. Based on the clinical suspicion or differential diagnosis, further biochemical and radiological investigations can be considered, as summarised in Table 3.

3. **Radiology**
   4. Gadolinium-enhanced pituitary MRI is considered as the preferred radiologic investigation of choice to define pituitary anatomy and appearances. The radiological features suggestive of hypophysitis include a prompt, intense and homogenously enhancing gland with no obvious stalk deviation. This is further supported by the absence of posterior pituitary bright spot, particularly, in patients presenting with diabetes insipidus. The lesions are commonly associated with symmetrical suprasella extension and enhancement of the adjacent dura referred as ‘dural tail’ (16). These features are most prominent in the patient with classical lymphocytic hypophysitis. IgG4 hypophysitis and immune checkpoint therapy-related hypophysitis

<table>
<thead>
<tr>
<th>Suspected conditions</th>
<th>Investigations</th>
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<tbody>
<tr>
<td>Lymphocytic hypophysitis</td>
<td>Thyroid antibodies (TPO)</td>
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<tr>
<td></td>
<td>Anti-nuclear antibody</td>
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<tr>
<td></td>
<td>Anti-Ro, anti-La, anti-SSa, anti-Ds-DNA (if concomitant autoimmune features present)</td>
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<tr>
<td></td>
<td>Pituitary antibody</td>
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<td></td>
<td>Chest X-ray, interferon gamma assay if history of travel and tuberculosis suspected</td>
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<td></td>
<td>Serum ACE levels if sarcoidosis suspected</td>
</tr>
<tr>
<td></td>
<td>ANCA antibodies</td>
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<tr>
<td></td>
<td>CSF analysis for glucose, protein, oligoclonal bands, ACE CT and scintigraphy</td>
</tr>
<tr>
<td>Granulomatous lesions</td>
<td>Immunoglobulin levels, particularly IgG4</td>
</tr>
<tr>
<td>IgG4-related disease</td>
<td>FDG PET for disease activity</td>
</tr>
<tr>
<td>Langerhan cell histiocytosis (LCH)/Erdheim–Chester disease (EDH)</td>
<td>Skeletal survey, whole body bone scan</td>
</tr>
<tr>
<td>Germinoma (if considered as differential to hypophysitis)</td>
<td>FDG PET for disease activity</td>
</tr>
<tr>
<td>Other infiltrative/infectious aetiologies</td>
<td>Serum and CSF AFP (alpha-fetoprotein) and HCG (human chorionic gonadotropin)</td>
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<td></td>
<td>LDH (lactic acid dehydrogenase), urine analysis</td>
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<tr>
<td></td>
<td>Imaging</td>
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<tr>
<td></td>
<td>CSF analysis (cytology, oligoclonal bands)</td>
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Table 3 Investigations for suspected hypophysitis (excluding histology).
have not been reported to have unique or distinctive radiological characteristics that facilitate clear categorisation. The characterisation of the unusual sella-based mass is not straightforward and generally results in a wide differential. Not uncommonly, the presence of an ‘empty sella’ has been considered as the atrophic response of the burnt out inflammatory process (17). To aid distinction between pituitary adenoma and hypophysitis, Gutenberg et al. derived a radiologic scoring system (18). They used relation to pregnancy, pituitary mass volume and symmetry, signal intensity and signal intensity homogeneity after gadolinium administration, posterior pituitary bright spot presence, stalk size and mucosal swelling for the calculation of the score (18). The score ranges from −13 to +8 and a score of ≥1 was suggestive of adenoma, whereas a score of ≤0 suggested hypophysitis. Despite the systematic scoring, the differentiation continues to remain difficult (5). In a recent systematic review, Catford et al. demonstrated that isolated PS lesions are more common in LCH, lymphocytic hypophysitis, germ cell tumours or metastases, but imaging in isolation does not differentiate between aetiologies (20).

5. If surveillance is the preferred initial management, then follow-up with 3–6 monthly or annual scans are used. A closer follow-up may be preferred when a suspected malignant lesion has not been ruled out. A significant proportion of lesions will progress. Jian et al. demonstrated changes to baseline images in 21 out of 37 PS lesions over a mean follow-up of 4.2 years (19). They recommended using progression of stalk thickness as a guide to consider pituitary biopsy.

6. In patients suspected to have secondary hypophysitis related to systemic pathology, additional imaging is helpful to identify other involved sites of disease. CT chest, abdomen and pelvis is useful in patients with potential sarcoidosis, TB, connective tissue disorders or when malignancy is a potential differential diagnosis. The introduction of FDG PET-CT has been helpful in confirming multisite disease and avoiding the need for pituitary biopsy in patients with IgG4-related disease and LCH (20, 21).

7. Immunology

8. Attempts to consistently identify autoantigens that can be implicated in the causation of hypophysitis have been unsuccessful (6, 9). Numerous researchers over the years have reported presence of possible antigens such as alpha enolase (22), secretogranin II (23), chromosome 14 open reading frame 166 (24), pituitary gland-specific factors (PGSF1a and PGSF2 (25) and pituitary-specific transcriptional factor 1 (26), but the pathogenicity of these antigens has not been confirmed. One study demonstrated anti-rabphilin-3A antibody in 76% (22/29) patients with central DI and suspected lymphocytic infundibular neurohypophysitis, suggesting a potential role as a future diagnostic biomarker (27).

9. Serum anti-pituitary antibodies have a low sensitivity and specificity and therefore are normally thought to be of limited use. Ricciuti et al. reviewed 122 articles using immunofluorescence-based testing methods and provided helpful guidance in the identification of pituitary antibodies (28). However Bellastella et al. recently suggested that looking for anti-pituitary antibodies may be helpful in selective situations such as patients with apparently idiopathic hypopituitarism with other autoimmune diseases, in patients with hyperprolactinemia without pituitary adenoma at MRI, without hypothyroidism or associated with iatrogenic causes or in patients with empty sella (5). Furthermore, in select cases, anti-hypothalamus antibodies may help to establish association of the presenting condition with a selective hypothalamic or pituitary autoimmune process (5). These tests are not currently part of routine practice. Other disease-specific antibodies (such as ANA, ds-DNA, ANCA) may be useful in the assessment of secondary hypophysitis.

10. Data from the Hopkins Hypophysitis Registry suggest that demonstrable co-existing autoimmune pathology in the patient with hypophysitis is uncommon with autoimmune thyroid disease (the commonest co-associate) present in only 8% of patients with autoimmune hypophysitis (4).

11. Histology

12. Histological assessment will provide confirmation and classification of hypophysitis and therefore is the most robust and definitive method of diagnosis. However, obtaining histology will require neurosurgical biopsy or resection of sella or suprasella tissue, and this potentially involves significant morbidity. Obtaining a tissue sample might also not be practical for other reasons, including spontaneous resolution or regression, response to initial medical management such as steroid therapy or difficulty in obtaining patient consent.

13. When available, evaluation of the histological specimen provides valuable information about the nature of the disease. Histologic stains to identify inflammatory cells and use of tissue (such as CD45 (leukocyte common antigen), CD3 (T-cells), CD20...
(B cells), CD68 (macrophages) and CD138 (plasma cells)) and hormone-specific immune staining helps to delineate different types of hypophysitis (29). The presence of histiocytes, granulomas xanthomas are essential to confirm specific subtypes of pituitary inflammatory lesions.

**Treatment of hypophysitis**

The natural history of hypophysitis is variable, and there is no strong evidence base for management recommendations. It is likely that increased understanding of the specific causal conditions and their treatment responses (e.g. IgG4-related disease, immune checkpoint inhibitor treatment) will emerge with future studies. Bellastella et al. distinguish between the acute phase of hypophysitis, which may require primary treatment; and a chronic or burnt out phase during which only treatment of hypopituitarism is needed (7). Hypopituitarism and diabetes insipidus should be treated according to conventional recommendations (30).

The main objectives of treatment are to manage pituitary hormone deficiencies and to reduce the inflammatory pituitary enlargement with associated mass-related consequences. Primary treatment of the hypophysitis falls into four categories which include: surgery, anti-inflammatory medical therapy, conservative management and radiotherapy. Historically, surgery remains the preferred method of choice (4) when there is significant mass effect. The advantages of surgery are that it provides a histological diagnosis to guide future management and excludes the diagnosis of tumour. It also reliably and quickly treats mass effects and visual impairment due to the lesion (31). In a large German cohort, surgery for hypophysitis resulted in significant resolution of symptoms such as headaches and visual disturbances (31, 32, 33). The rate of recurrence of the lesion after surgery was reported to be 11–25% (31, 32). Post-operative follow-up showed the development of pituitary insufficiencies and was particularly frequent after gross total resection compared to biopsy or partial resection.

There are limited reports of spontaneous resolution of hypophysitis. In cases without significant mass effect or headache, surveillance of hypophysitis can be used in addition to replacement of endocrine insufficiencies (31, 34).

Glucocorticoid therapy forms the cornerstone of medical management. Numerous authors have confirmed an initial good response to ‘steroid therapy’, but the overall recurrence rate has been reported to be high and highlights the limitations of this treatment (33, 35). Up to 38% patients developed relapse on steroid therapy, in a recent large cohort (31). As is expected, treatment with long-term steroids leads to increasing adverse effects and limits the use of this strategy (31). In cases with progressive or recurrent disease steroid-sparing options such as alternative immune-suppressive agents or radiotherapy have been considered. A variety of agents have been used, and experience often reported as case reports. Supplementary Table 4 (see section on supplementary data given at the end of this article) provides a brief summary of the papers reporting use of steroid-sparing therapies. The last few years have seen a rise in the use of immunosuppressive therapies for resistant lesions (36). Azathioprine is the most commonly used immune-suppressive agent at present, while in the coming years, it is likely we will see more focussed monoclonal antibody-directed therapy such as rituximab (31).

Hyperprolactinaemia affects a minority of cases in the acute phase of the pituitary inflammation (5). Some authors have reported the possibility of prolactin modulating autoimmunity and the use of dopamine agonists for inducing treatment response (37, 38). While the beneficial effect of long-term dopamine agonist treatment is still uncertain (5), the use of cabergoline/bromocriptine in hyperprolactinaemic patients is likely to provide symptomatic relief (from galactorrhoea and/or diabetes insipidus). Mass effect with visual consequence may be present. Both genders and all ages may be affected but the condition is classically identified during pregnancy or early post-partum (2). The diagnosis is confirmed histologically and the features include normal pituitary with lymphocytic infiltration, plasma cells, histiocytes and fibrosis. Treatment includes replacement of hormone deficiency (including ADH) and decision making regarding conservative,
Hypophysitis

**Management algorithm for the patient with hypophysitis**

**Clinical Suspicion of hypophysitis**
- Headache & hypopituitarism
- Pregnancy & pituitary disease
- Known IG4-RD
- Immunotherapy
- Previous hypophysitis

**Pituitary mass lesion**
- Characteristic features of hypophysitis (MRI)
  - Hypopituitarism/especially DI
  - Incidental sella mass in patient on immunotherapy

**Clinical Scenario**

**Investigations**
- History and examination, Pituitary MRI (gadolinium-enhanced)
- Full pituitary blood profile (incl electrolytes and osmolalities)
- sACE, antibodies (pituitary, ANCA, ds-DNA), serum IgG4

**Diagnosis**
- Consider whole body cross-sectional imaging ± FDG PET, with tissue biopsy if indicated

**Hypophysitis**
- Consider biopsy of sella / suprasella mass lesion

**Management**

**Follow-up**
- Early assessment for treatment response with pituitary MRI. Follow with serial imaging until clear stability, maintain clinical suspicion for recurrence. Consider escalating to immunosuppression or radiotherapy if persistent symptoms or continuing mass effect despite corticosteroids ± surgery.

**Figure 1**

Early assessment for treatment response with pituitary MRI. Follow with serial imaging until clear stability, maintain clinical suspicion for recurrence. Consider escalating to immunosuppression or radiotherapy if persistent symptoms or continuing mass effect despite corticosteroids ± surgery.

Medical and surgical therapies. High-dose suppressive glucocorticoid remains the cornerstone of medical therapy but a variety of immunosuppressive treatments have been used. Surgery is indicated for non-responders, mass effect, headache, visual failure or when a tissue diagnosis is considered important. Radiotherapy may be useful when there is relapse of disease and some patients require multi-modal treatment. There have been comprehensive reviews of LH and we have purposefully limited the discussion (1, 3, 4, 5) in this review.

3. **Granulomatous hypophysitis**
4. Granulomatous hypophysitis is the second commonest type of primary hypophysitis (10). Granulomatous disease can be seen as a primary entity (known as idiopathic primary granulomatous hypophysitis) or secondary to a systemic pathology such as sarcoidosis, tuberculosis or granulomatosis with polyangitis (previously known as Wegener’s granulomatosis). In less than a hundred reported cases of the primary condition, five have been associated with the post-partum state (39). The histology is characterised by the presence of multinucleated giant cells, histiocytes, lymphocyte infiltration along with plasma cells (40). It is still unclear if granulomatous changes form a continuum of the lymphocytic inflammatory processes (33). There has been reported female predominance in a systematic review of idiopathic cases (40). The clinical presentation tends to be more severe with higher incidence of visual symptoms compared to LH (10, 40). In a review of 31 patients, Gutenberg et al. identified that gonadotrophin deficiency was present in 100% cases with granulomatous disease (33). Systemic symptoms such as a fever, nausea and vomiting were reported to correlate with earlier presentation (40). The radiological appearance does not help differentiate between different types. The presence of immunological markers of systemic conditions can help identify the secondary granulomatous disease (Table 3). Glucocorticoid therapy appears to be less effective compared with LH (33) while surgical resection leads to better symptom resolution (40).

5. **Xanthomatous hypophysitis**
6. Xanthomatous hypophysitis (XH) is considered to be the rarest of the histological types. Only 18 cases...
have been reported since the first published in 1998 (41, 42). It is unclear if XH constitutes a distinct entity or is a possible extension of the autoimmune or lymphocytic spectrum. As seen with xanthomatous lesions elsewhere in the body, it is postulated that xanthomatous infiltration results from macrophage activation secondary to chronic inflammation (42). It has been more commonly reported in females (43). The clinical presentation is thought to be similar to LH, but visual symptoms are considered to be rare (33, 43). The clinical symptoms appear to be milder and present for a longer duration in the patients compared to other types of hypophysitis (33). Similarly, DI is rarely reported with xanthomatous presentation (33).

7. Xanthomatous lesions present radiologically as cystic sellar masses on MRI and enhance on the post-gadolinium contrast images. The gross lesion appears as a cyst filled with thick orange coloured fluid with floating crystals (42, 43). The diagnosis is only confirmed on tissue sections demonstrating xanthoma cells or lipid-laden macrophages in the pituitary tissue. Immunostaining highlights CD68 glycoprotein and can be utilised as tool to mark macrophage-related pathology (42, 43). It has been suggested that XH may be less responsive to steroid therapy, as compared to LH but as clinical experience is extremely limited this is yet to be established. Given the reported lack of effectiveness of medical management, most lesions are treated with surgery, if not already operated on for diagnostic purposes (42). The response to treatment varies from complete, partial or no recovery from mass effect of symptoms, but endocrine deficiencies seldom recover (44, 45).

8. IgG4-related disease

9. IgG4-related hypophysitis was first reported in 2004 (46). It is believed to be rare but a recent retrospective histological review of cases, previously thought to demonstrate LH showed that 41% (12/29) were reclassified as IgG4 hypophysitis (47). The previous lack of recognition of this aetiology indicates that cases previously classified as ‘hypophysitis’ or ‘lymphocytic hypophysitis’ may in fact reflect IgG4-RD. It is likely that further retro- and prospective studies will help us understand whether IgG4-RD represents a substantial cohort within the hypophysitis spectrum of diseases. While the exact aetiology still remains unclear, an association with autoimmune and atopic conditions has been frequently reported (48, 49). In a recent paper, Della Torre et al. debated against the role of atopy in IgG4 disease, which remains to be confirmed (49, 50). The exact role of IgG4 in pathogenesis remains elusive, and it may well be considered a ‘bystander’ in the inflammatory phenomenon (51).

10. The condition commonly presents as pseudo-tumour lesions with IgG4-dominant plasmacytic infiltration of multiple organs (52, 53, 54). IgG4-related disease has been more commonly reported in middle-aged and elderly populations, with male predominance (48, 54, 55), except for a recent study where authors suggested a distinct subset of IgG4 disease with female predominance (47). The commonest co-existent IgG4-related pathology associated with pituitary disease is retroperitoneal fibrosis (56).

11. A consensus statement described histological findings of IgG4-related disease and a prerequisite criteria with two out of the three features namely, dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis. There have been other disease-specific guidelines, which report exceptions to these guidelines (47, 57). Leporati et al. suggested a pituitary disease-specific diagnostic criteria for confirmation of the disease (52). In a retrospective review of primary hypophysitis, Bernreuther et al. suggested that presence of lymphoplasmacytic infiltrate should be used as a prerequisite to test for IgG4 staining. The presence of more than ten IgG4-positive cells per high power field and a ratio of IgG4/IgG-positive cells of more than 40% was noted in all patients with confirmed IgG4 hypophysitis (47). These findings have been debated by others (58).

12. Serum levels of IgG4 are not sensitive or specific for IgG4-RD and elevated levels tend to normalise with steroid therapy making them less useful as diagnostic tool (56, 58). It is recommended that laboratories reporting IgG4 should confirm freedom from prozoning (hook) effect (59). Wallace et al. suggested that those with elevated serum IgG4 could represent a subset of patients with multi-organ involvement (60). In a recent report, Landek-Salgado et al. demonstrated autoantigens against growth hormone and POMC in a biopsy proven IgG4-hypophysitis patient (61). The significance of the finding or its applicability to other types of hypophysitis is uncertain. The radiologic features are not distinct from other types of hypophysitis. There is an evolving role of the use of FDG PET in IgG4-related disease to characterise systemic involvement of tissues. Steroids form the mainstay of treatment with a beneficial early response, but recovery of endocrine function is thought to be
uncommon (56). There is a potential role for the use of B-cell-depleting therapies (62, 63).

13. **Langerhans cell histiocytosis**

14. LCH is a rare inflammatory disease, with an incidence of 1–2 cases per million in adults (64, 65), though it is more commonly reported in the paediatric population. The exact pathogenesis of the condition is still debated. It has a variable unpredictable course, often ranging from a self-limiting course to a rapidly progressive form (66). Often diabetes insipidus is one of the earliest manifestations, denoting the predilection for involvement of the hypothalamic–pituitary axis (65). Anterior pituitary deficiencies are less common, but nonetheless have been reported in approximately 20% of patients (66). Growth hormone deficiency is most common, followed by gonadotrophin deficiency, as reported in paediatric studies (67, 68). Prolactin elevation is considered as a possible result of stalk involvement (69), with disinhibition. Patients with multisystem involvement are more likely to have DI associated with multiple endocrine insufficiencies.

15. Diagnosis is suspected when there are other multisystem features or the presence of diabetes insipidus. While confirmation of the diagnosis is based on histological and immunological criteria (Table 3), a skeletal survey and chest X-ray could be the first-line imaging investigations (66). MRI findings are not specific to LCH, and different patterns of pituitary involvement have been reported. While absence of posterior pituitary bright spot is most common, other features such as stalk thickening, pituitary enlargement, empty sella and hypothalamic involvement have all been described (65). PET imaging may be used to guide response to therapy or identification of active disease (66). It also has a role in allowing clarification of the diagnosis by identifying sites of disease more amenable to biopsy than the pituitary gland. Treatment commonly involves an immune-suppressive regimen, chemotherapy or radiotherapy and unlike in children, it has not yet been standardised for adult patients (66). Hormone replacement therapies should be initiated as soon as the diagnosis is established. Vinblastine and steroid-based therapy are suggested as the first-line options by the Histiocyte Society Guidance (70). An initial 6-week induction regimen is followed by 12 months of maintenance therapy to reduce the risk of reactivation (70). Radiotherapy (lower doses than for pituitary adenoma) results in partial or transient resolution of radiological abnormalities (65). While the radiological lesion seems to regress with treatment, recovery of endocrine deficiencies is rare (71). New-onset DI, in a patient previously considered to be in remission, might be a sign of reactivation of the disease (65).

16. **Immune checkpoint therapy-related hypophysitis**

17. With the introduction of novel immune-targeted therapy for a variety of cancers, there has been a rise of immune-mediated systemic adverse events. Ipilimumab (CTLA4 antibody) was the first immune checkpoint inhibitor licensed for the use in malignant melanoma (72). More recently nivolumab (PD1 antibody), pembrolizumab (PD1 antibody) and combination therapies are being used for a number of metastatic malignancies. Hypophysitis is recognised as side effect of these agents (73). Pituitary inflammation with immune checkpoint inhibitor-related therapies appears to have a higher incidence in males and the elderly, unlike LH (74). The incidence is commonly noted prior to the third cycle of treatment and ranges from 5 to 36 weeks from the onset of the oncological therapy, with a mean duration of 9 weeks (75).

The clinical presentation is similar to other forms of hypophysitis, in relation to the symptoms and requires a high index of suspicion. Headache has been reported in several studies. All patients receiving immune checkpoint therapy with new onset headache or suspected cortisol deficiency should be evaluated for the likelihood of hypophysitis (76). Caturegli et al. have recently summarised the differences between immune checkpoint therapy (CTLA-4)-induced hypophysitis and primary (lymphocytic) hypophysitis (76). The incidence of visual disturbances and diabetes insipidus is extremely rare (73, 76). Endocrine deficiencies are noted in more than 70% patients and include high rates of thyrotrophin, gonadotrophin as well as corticotroph insufficiency (77). Little is known about GH status. While the trend to recovery is very variable in most primary hypophysitis, recovery of ACTH insufficiency is very rare in CTLA-4-induced hypophysitis (76, 77).

18. There are no obvious radiological patterns, which differentiate primary and drug-induced hypophysitis and as has been reported, the radiological findings can precede clinical diagnosis by several weeks (74). The use of FDG PET in these oncology patients has a potential to identify radiological evidence of additional sites of immune-mediated adverse effects. Numerous case reports highlighted the incidental detection of hypophysitis, pancreatitis, adrenalitis...
and thyroiditis, when PET was used for surveillance purposes (78, 79, 80, 81).

19. Caterugli et al. have described the biopsy findings of CTLA-4 related hypophysitis (76). They have demonstrated pathological findings of complement fixation, macrophage infiltration and lymphocyte activation confirming that the mechanism of CTLA-4-related hypophysitis is largely a result of type II and type IV hypersensitivity reaction. Iwama et al. were the first to report to the presence of CTLA-4 Ag in pituitary tissue and suggest antibody-dependent complement activation (ADCC) as the underlying model of immune activation (82). Nivolumab and pembrolizumab are IgG4-based PD1 antibodies and less likely to be able to mount a similar ADCC-mediated response (83). PD1 expression on pituitary cells has not been investigated. Further details of the mechanism are beyond the scope of this review and increased understanding of the precise pathophysiological mechanism(s) responsible for immune therapy-related hypophysitis is required.

20. The management of immune checkpoint therapy-related hypophysitis depends on the severity of the clinical presentations graded by the CTCAE grading system in oncology trials (73). For milder dysfunction, the treatment involves replacing the hormone deficiency as standard (73). But in severe or life-threatening cases, the role of high-dose steroids and discontinuation of the oncology therapy needs consideration (73, 84). Many centres are developing local guidelines to help clinicians identify iRAEs and manage acute and chronic complications of immune checkpoint therapies.

Recent advances in the understanding of hypophysitis: imaging modalities and immunomarkers

In recent years, a novel entity called ‘Anti-Pit 1 antibody syndrome’ has been recognised (85). This presents as an acquired deficiency of growth hormone, TSH and prolactin with detectable anti-Pit 1 antibody (26). It is considered to be a cytotoxic T cell-mediated autoimmune process, but further studies are needed to establish the exact pathogenesis (86). Similarly antibody to pituitary tissue has been identified as a possible antigenic target in LH, even in patients not presenting with ACTH deficiency (87). Heaney et al. have suggested that use of HLA markers for DQ8 and DR53 could be used to identify patients suspected to have LH. There is a 23.1-fold increase in the levels of DQ8 in the patients with LH as compared to those with other pituitary lesions (88).

The use of nuclear medicine in the diagnosis of inflammatory conditions has been evolving. Recently Lee et al. used FDG PET in IgG4-related diseases. They reported that pattern of uptake and multi-organ involvement were significant predictors of IgG4-related disease (89). The use of software-based image processing technology called textural analysis has been suggested to differentiate neoplastic and non-neoplastic PS lesions with more certainty. The distribution of the grey levels in the given region of interest could be used as a guiding tool to determine, which lesions are less likely to be inflammatory and facilitate decision making (90). In clinical practice, FDG PET has become an increasingly used tool in the assessment of the patient with inflammatory pituitary conditions, often allowing diagnosis to be made by facilitating less invasive tissue biopsy in multisite disease.

Anticipated future developments

Interest in inflammatory disorders affecting the pituitary gland has increased in recent years. Recognition of IgG4-RD has prompted reconsideration of the classification of hypophysitis and clinicians are considering this diagnosis both in new prospective cases and in historic ones labelled as LH (often without biopsy). The advent of immune checkpoint inhibition has meant an increase in clinical experience with hypophysitis for endocrine physicians and provides insight into the pathophysiological mechanisms of disease. These increases in understanding will likely result in new diagnostic algorithms and more accurate classification of disease. New serological markers are likely to emerge and non-invasive diagnostics will improve. The near future will likely see more accurate diagnosis of primary and secondary hypophysitis and lead to more consistent and specific treatments for this rare group of disorders. Collaborative multi-centre prospective studies are required to define the optimal treatment approaches for the patient with hypophysitis.

Supplementary data
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Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.


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