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Review article

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An update on hypophysitis

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Abstract

Hypophysitis is defined by inflammation of the pituitary gland and/or infundibulum. It can cause headaches and symptoms due to hypopituitarism. Diagnosis is based on a combination of hormonal and imaging parameters but can, in individuals with an uncertain diagnosis, require a transsphenoidal biopsy. While the risk of immune checkpoint inhibitor-induced hypophysitis is well known, several aetiologies of secondary hypophysitis have been identified and hypophysitis can also occur in relation to pregnancy. Primary hypophysitis is defined by the absence of a secondary cause of hypophysitis. Although each subtype can present with distinct clinical, endocrine and radiological features, extensive overlap makes the aetiological diagnosis difficult. Management of hypophysitis is another challenging task. Whereas some studies have suggested that high-dose glucocorticoids can improve pituitary function and alleviate symptoms, others have found limited benefit. Immunosuppressive agents have also been used as targeted therapy for the underlying condition or in individuals with aggressive hypophysitis, potentially improving both clinical presentation and hormonal function. These therapeutic approaches, used alone or in combination, can be considered in selected patients with primary, pregnancy-related or secondary hypophysitis. The aim of this comprehensive Review is to critically analyse the positive and aetiological diagnostic steps and the management of all subtypes of hypophysitis.

Sections

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Review article

Key points

- The diagnosis of hypophysitis is based on histopathological documentation. However, radiological (MRI appearance), biological (anterior pituitary deficiency, hyperprolactinaemia, confirmed vasopressin deficiency) and/or clinical (headache, visual impairment) evidence can be sufficient.
- Hypophysitis typically presents on MRI with a moderate increase in glandular size with homogeneous enhancement, suprasellar extension, thickening of the pituitary stalk and loss of the posterior pituitary T1-W bright spot.
- Hypophysitis can be the first manifestation of systemic disease (sarcoidosis, L-group histiocytosis, IgG4-related disease). It is important to screen for systemic disease at diagnosis and to repeat screening over time.
- Anti-CTLA4 and anti-PD1–PDL1 therapies are immune checkpoint inhibitors that can cause hypophysitis. In patients receiving these treatments, pituitary function needs to be monitored regularly.
- Glucocorticoids are the therapy that has shown the most evidence of efficacy in hypophysitis. They appear to prevent endocrine deterioration and improve headaches, but their effect on visual pathway compression needs to be clarified.

Introduction

The first reported case of hypophysitis was in 1962, in a 22 year-old woman who died of postpartum adrenal crisis[1]. Since then, and especially with the advent of immune checkpoint inhibitors (ICIs)[2,3], the incidence of hypophysitis has increased dramatically[2,4]. We now know that hypophysitis can be related to pregnancy[5], or precede or be diagnosed during the course of systemic diseases[6] such as sarcoidosis[7], L-group histiocytosis[8,9] and, more recently, IgG4-related disease[10]. These infiltrative diseases are characterized, respectively, by non-necrotizing granulomatous inflammation[11], accumulation of dendritic cells and/or macrophage-derived cells[12], and infiltrates of IgG4-positive plasma cells[13]. A few years ago, paraneoplastic autoimmune hypophysitis was also described[14]. Finally, primary hypophysitis, the most well-known form, can occur spontaneously, presumably due to autoimmunity[15]. While the procedures to diagnose primary hypophysitis can be challenging, and successful diagnosis sometimes requires repeated evaluations over several years to ascertain the 'primary' nature of the condition, the management is at least as complex. Indeed, apart from the management of ICI-induced hypophysitis, which is now well defined[2], the treatment of the other aetiologies of hypophysitis remains a matter of debate. However, the growing number of cases of hypophysitis identified through improvement in diagnostic procedures means that there is a need for several specialists to try to better understand the epidemiology, diagnostic steps and management possibilities for this complex disease. The aim of this comprehensive Review therefore is to critically analyse the positive and aetiological diagnostic steps, providing a detailed overview of the different subtypes of hypophysitis. We also highlight the main characteristics that enable identification of a particular aetiological subtype. The final part of the article focuses on the management of all subtypes of hypophysitis, adding some advice coming from our multidisciplinary experience.

Definition and epidemiology

Hypophysitis is characterized by inflammation of the pituitary gland and/or the pituitary stalk. While the diagnosis has long been based on histological evidence, it is now usually based on a combination of clinical, biochemical and radiological findings.

The epidemiology of hypophysitis is unclear except for ICI-induced hypophysitis. In the past 10 years, the incidence of ICI-induced hypophysitis has been frequently studied, and ranges from 0.6% to 20% of patients treated with ICIs[16,17]. Data on the other aetiologies of hypophysitis are scarce. The estimated prevalence of hypophysitis from 20 years ago of one in nine million people was probably an underestimate because imaging techniques, which are crucial for the positive diagnosis of hypophysitis, were not as effective as they are today[18]. More recently, in a 2010 study, the prevalence has been estimated at one in five million[19]. Several surgical series have reported that hypophysitis accounts for 0.3–1.0% of pituitary surgical procedures[19–24], 0.5% of hypopituitarism cases[19] and 2.0% of non-functioning macro lesions[19].

Several distinct classifications of hypophysitis can be used (Fig. 1). First, hypophysitis is classified anatomically as adenohypophysitis (damage to the anterior pituitary gland), neuroinfudibulohypophysitis (damage to the posterior pituitary gland and the pituitary stalk) and panhypophysitis (damage to the entire pituitary gland). Second, hypophysitis is classified histologically as lymphocytic, granulomatous, xanthomatous, xanthogranulomatous and IgG4-associated hypophysitis[10,25,26]. Third, hypophysitis is classified aetiologically as primary, pregnancy-related, secondary and paraneoplastic hypophysitis. Several causes of secondary hypophysitis can be identified: iatrogenic disease, which is usually (but not exclusively) induced by ICIs, and systemic disease, which is mainly due to immune system dysregulation (mainly sarcoidosis or IgG4-related disease), clonal cell expansion (mainly L-group histiocytosis), or infection (mainly syphilis or tuberculosis).

Hypophysitis can be the first symptom of a systemic disease, sometimes appearing several years before other manifestations[6]. Pregnancy-related hypophysitis usually occurs in the months before or after childbirth. Primary hypophysitis is a diagnosis of exclusion: secondary causes must be systematically ruled out, first at diagnosis and then during follow-up, as we discuss in the following paragraphs. In this Review, we deign as 'non-iatrogenic hypophysitis' a large group of aetiologies of hypophysitis including primary hypophysitis, pregnancy-related hypophysitis, secondary hypophysitis due to systemic diseases and paraneoplastic hypophysitis. These different aetiological subtypes are characterized by slightly different clinical, endocrinological and MRI presentations, but overlaps are common (Supplementary Table 1). The sex ratio and age at onset of hypophysitis vary according to this aetiological subtype (Supplementary Table 1).

Diagnosis

Positive diagnosis of hypophysitis

Clinical symptoms. The clinical symptoms of hypophysitis are variable. The most common symptom is headache, which occurs in 38–76% of patients[6,21,27–32]. In cases of locoregional invasion (that is, when pituitary hyperplasia compresses the optic chiasm), disturbances affecting the visual pathways can be observed, and have been reported in 11–52% of patients[21,27,28,30–34]. These disturbances include visual field defects (from exclusion of the blind spot to quadranopia (loss of a temporal

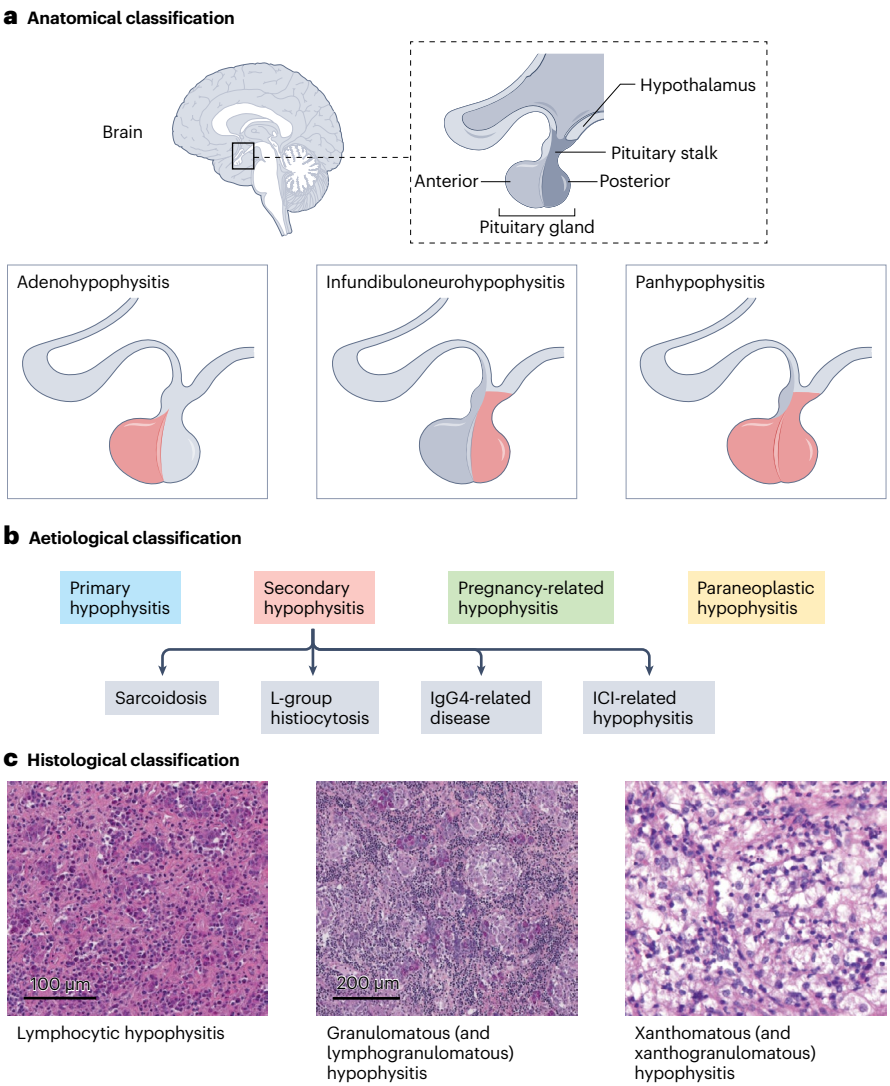

Fig. 1 | Classification of hypophysitis. **a**, Anatomical classification. Hypophysitis can affect the anterior pituitary alone (adenohypophysitis), the posterior pituitary and pituitary stalk (infundibuloneurohypophysitis) or the entire pituitary gland (panhypophysitis). **b**, Aetiological classification. Hypophysitis can be categorized as primary, secondary, pregnancy-related or paraneoplastic. Secondary hypophysitis is predominantly caused by sarcoidosis, L-group histiocytosis, IgG4-related disease or immune checkpoint inhibitor (ICI) therapy. **c**, Histological classification. Hypophysitis can be classified as lymphocytic, granulomatous (or lymphogranulomatous) (shown using haematoxylin phloxine saffron staining) or xanthomatous (or xanthogranulomatous). The right image in part **c** is reprinted from ref. 45, CC BY 4.0.

fourth of the visual field), hemianopia (loss of the temporal half of the visual field) or loss of visual acuity), or, less commonly, oculomotor palsy. In individuals with hypothalamic infiltration, disturbances in satiety (resulting in rapid weight loss or gain) or body temperature (hypothermia or hyperthermia) can be observed. This very rare situation is defined as hypothalamitis, and might or might not be associated with hypophysitis[35].

Lastly, clinical symptoms can be due to endocrine deficiencies or hyperprolactinaemia due to pituitary stalk compression. These symptoms can include fatigue, decreased libido, galactorrhoea, nausea, amenorrhoea and polyuria–polydipsia syndrome[36].

Pituitary deficiency and hormonal measurements. Infiltration or inflammation can cause various pituitary dysfunctions, including anterior or posterior deficits, and hyperprolactinaemia (due to stalk compression) or less commonly hypoprolactinaemia. The most common anterior pituitary deficiency is corticotroph deficiency (in up to 60%), followed by thyrotroph deficiency and gonadotroph deficiency (in 30–60%). Arginine–vasopressin (AVP) deficiency (previously known as diabetes insipidus) has been reported in 50% of cases.

As is discussed later in each section, different hormonal profiles can indicate specific systemic diseases in secondary hypophysitis. These profiles are also important when considering the risks of late-onset pituitary deficiency or the chances of long-term recovery. However, all patients with a suspected diagnosis of hypophysitis should have a complete hormonal evaluation. This evaluation should include assessment of 8.00 a.m. levels of adrenocorticotropin hormone (ACTH) and cortisol, levels of thyroid-stimulating hormone (TSH) and free thyroxine, luteinizing hormone, follicle-stimulating hormone, prolactin, and testosterone in men or oestradiol in women (except in women with regular menses or menopause). Levels of IGF1 can be difficult to interpret in patients with sometimes altered general condition such as weight loss and denutrition. The diagnosis of growth hormone (GH) deficiency should, however, be based on a stimulation test such as insulin tolerance test[37]. Finally, AVP deficiency should be investigated by looking for polyuria (>40–50 ml/kg per 24 h) and polydipsia

(>3 l/day), and possibly by determining urine osmolality and blood levels of sodium[36].

Imaging. Hypophysitis typically presents on MRI as a moderate increase in pituitary gland size, with homogeneous enhancement and suprasellar extension (adenoma-like pattern)[38]. Less commonly, it can present as an asymmetrical enlargement with heterogeneous enhancement[38–40]. The increased in pituitary gland size is often associated with thickening of the pituitary stalk, which can be isolated in one-third of patients[15], and loss of the posterior pituitary T1-W bright spot. These signs are the most characteristic features of hypophysitis[39,41].

Pituitary inflammation can extend beyond the gland, with mucosal thickening of the sphenoid sinus and adjacent dural thickening. Dark signal intensity areas on T2-W images around the pituitary gland, described as the parasellar T2 dark sign[42], might be seen in chronic forms associated with fibrosis. The chronic course usually leads to atrophy in the form of an empty sella.

Imaging does not clearly distinguish between different aetiologies of hypophysitis, particularly in the absence of extrapituitary radiological findings. However, some presentations are more common in clinical practice. Lymphocytic hypophysitis usually presents with the typical findings of hypophysitis, that is gland enlargement and homogeneous enhancement. Granulomatous hypophysitis, often secondary to sarcoidosis, results in extensive hypothalamic–pituitary involvement with leptomeningeal infiltration[43,44]. In addition to sarcoidosis, any radiological abnormality of the central nervous system, such as leptomeningeal thickening and enhancement, should prompt evaluation for secondary causes of hypophysitis, particularly tuberculosis, syphilis or IgG4-related disease[13]. The rare xanthomatous form can present with cystic changes[45]. Finally, ICI-induced hypophysitis forms can present with normal findings on MRI, classic non-specific findings or subtle changes that are more visible when compared with MRI images from before therapy (Fig. 2).

The MRI protocol should include high-resolution (≤1 mm) isotropic 3D acquisition for a detailed view of the pituitary stalk, pituitary gland and parapituitary environment. The pre-contrast T1-W acquisition, particularly with fat signal saturation, is useful for detecting the presence or absence of the posterior pituitary T1-W bright spot. It seems reasonable to recommend cerebral MRI in conjunction with the pituitary MRI.

Histopathological findings. A biopsy of the pituitary gland or stalk can confirm hypophysitis. Although a biopsy remains the gold standard for confirming the diagnosis, it is rarely performed, as it often provides no additional information over standard diagnostic procedures, rarely alters management, and carries the risk of inducing pituitary

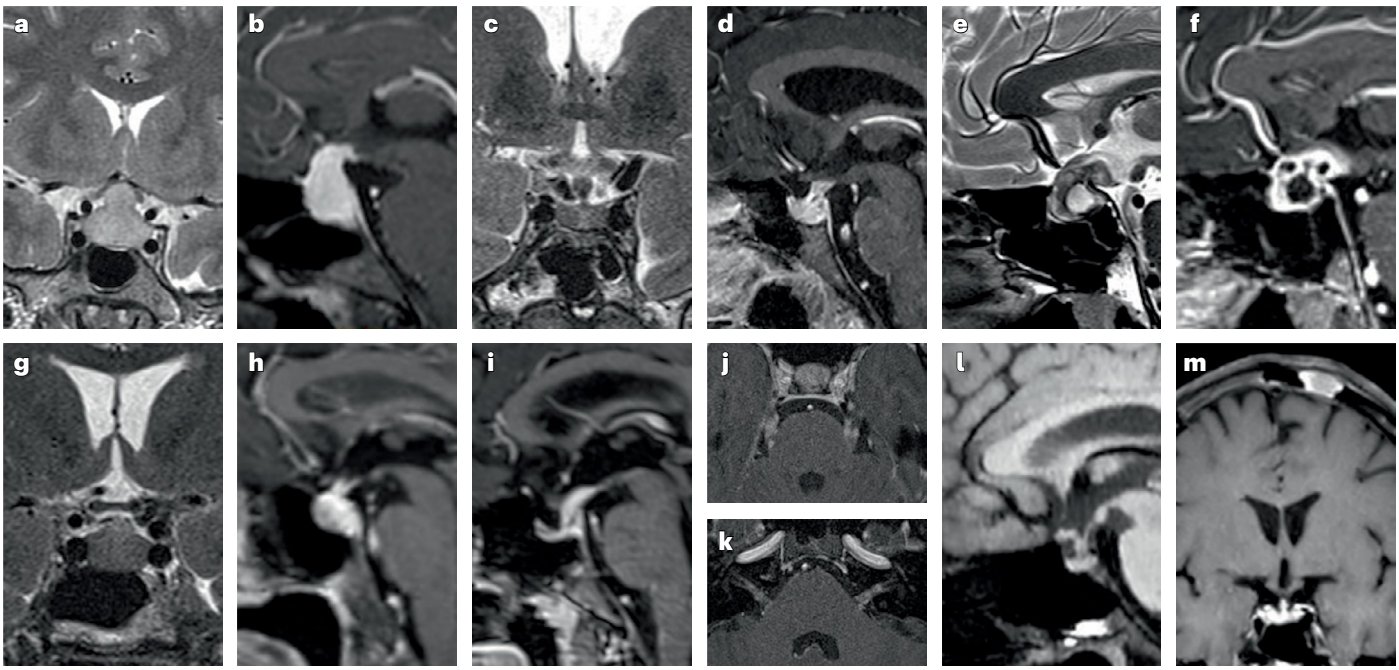

Fig. 2 | Primary and secondary hypophysitis. Adenoma-like lymphocytic hypophysitis in a 25-year-old woman (parts **a** and **b**) shows enlargement of the pituitary gland with suprasellar extension and hypersignal on the coronal T2-W image (part **a**), mimicking an adenoma but with symmetrical enlargement and strong homogeneous enhancement on the sagittal post-contrast T1-W image (part **b**). Primary infundibuloneurohypophysitis in a 28-year-old woman (parts **c** and **d**) shows thickening of the pituitary stalk on the coronal T2-W image (part **c**) associated with an enlargement of the posterior pituitary gland on the sagittal post-contrast T1-W image (part **d**). Panhypophysitis in a 47-year-old woman with inconclusive histology (parts **e** and **f**) shows enlargement of the pituitary gland and pituitary stalk with cystic and/or necrotic changes on the sagittal T2-W image (part **e**) and the sagittal post-contrast T1-W image (part **f**). Immune checkpoint inhibitor-induced hypophysitis (anti-PD1 and anti-CTLA4 therapy combined) in a 61-year-old woman with enlargement of the anterior pituitary (parts **g** and **h**) shows no involvement of the pituitary stalk on the coronal T2-W image (part **g**) and the sagittal post-contrast T1-W image (part **h**). Infundibuloneurohypophysitis in a 29-year-old man with sarcoidosis (parts **i**–**k**) shows linear thickening of the pituitary stalk and tuber cinereum on the sagittal post-contrast T1-W image (part **i**) and associated leptomeningitis of the cranial nerves on the axial post-contrast T1-W images (parts **j** and **k**). Langerhans cell histiocytosis in a 38-year-old woman presenting with arginine–vasopressin deficiency (parts **l** and **m**) shows loss of the posterior pituitary bright spot on the sagittal T1-W image (part **l**), thickening of the pituitary stalk and left lytic lesion of the cranial bone; part **m** shows the right craniotomy flap after surgical biopsy.

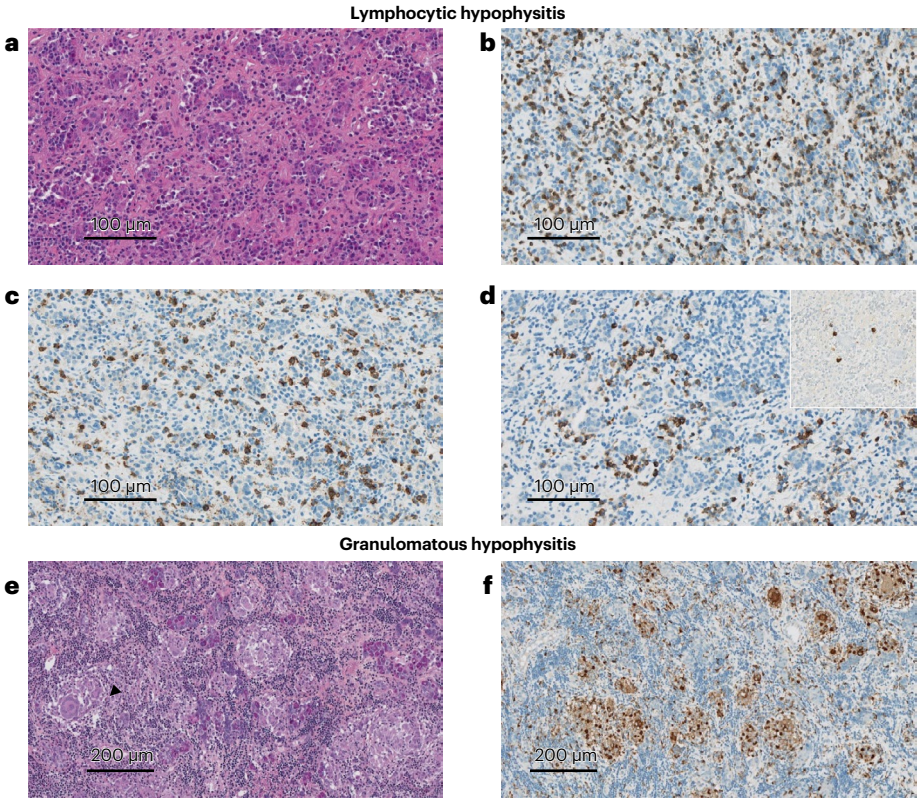

Fig. 3 | Pathology of hypophysitis. In lymphocytic hypophysitis, haematoxylin phloxine saffron (HPS) staining (part **a**) shows infiltration of the pituitary parenchyma by chronic inflammatory cells associated with fibrotic tissue remodelling. Immunohistochemical analysis (parts **b**–**e**) shows a polymorphic inflammatory infiltrate composed of $CD3^+$ T cells (part **b**), $CD20^+$ B cells (part **c**) and plasma cells (part **d**), without IgG4 overexpression (inset in part **d**). In granulomatous hypophysitis, standard HPS staining (part **e**) shows destruction of the pituitary parenchyma by epithelioid giant cell (arrowhead) granulomas, without necrosis. Immunohistochemical staining for CD68 (part **f**) shows the nodular granulomatous organization of histiocytic cells.

deficiencies. Histopathological examination can help distinguish between primary and secondary forms of hypophysitis and identify subtypes such as lymphocytic, granulomatous and xanthomatous variants[10,25,26].

Treatment approaches remain largely similar across these forms, although these subtypes exhibit distinct histological features. Lymphocytic hypophysitis (Fig. 3a–d) is characterized by diffuse lymphocytic infiltration. Plasma cells, a differentiated type of lymphocyte, can also be present, in which case the term 'lymphoplasmocytic' form can be used. When abundant, specific IgG4 staining can provide valuable diagnostic information in the setting of IgG4-related hypophysitis. Granulomatous hypophysitis (Fig. 3e,f) is characterized by granulomas with multinucleated giant cells. These granulomas can also contain lymphocytic infiltration, in which case the term 'lymphogranulomatous' form can be used, although the nosological classification remains granulomatous hypophysitis. Xanthomatous hypophysitis is characterized by foamy histiocytes[45]. Occasional granulomas can be observed; in such cases, the term 'xanthogranulomatous' form can be applied, although the condition is still classified as xanthomatous hypophysitis.

Histologically, primary and pregnancy-related hypophysitis are most often associated with lymphocytic or granulomatous inflammation, whereas secondary forms more commonly exhibit granulomatous or xanthomatous patterns. However, IgG4-related hypophysitis is a notable example of a type of secondary hypophysitis that typically presents as a lymphocytic form (Fig. 1c). Furthermore, xanthomatous hypophysitis can also arise as a reaction to a Rathke cleft cyst[46].

Biopsy findings can identify secondary causes of hypophysitis, such as tuberculosis (granulomas with caseous necrosis or *Mycobacterium tuberculosis*), L-group histiocytosis (histiocytic infiltration with *BRAF* or MAP kinase mutations) or IgG4-related disease. Tailoring treatment requires identifying these causes. This identification can often be achieved without resorting to pituitary biopsy.

Antibodies. Several antibodies can be looked for when diagnosing hypophysitis, including anti-pituitary antibodies and anti-hypothalamic antibodies. These antibodies are non-specific as they can be found in various conditions, including traumatic brain injury[47], autoimmune endocrine diseases and pituitary adenoma, and even in healthy individuals[48]. The anti-rabphilin 3A antibody is detected in most individuals with non-iatrogenic hypophysitis; however, it can also be found in 12–14% of healthy individuals and in those with other autoimmune diseases[49]. Although circulating anti-pituitary antibodies have been described as a marker of hypophysitis for more than 30 years[50], their measurement is not recommended in daily practice owing to a lack of specificity. The role of anti-Pit1 antibody is described in the section 'Paraneoplastic hypophysitis'.

Differential diagnosis on MRI

The differential diagnosis of hypophysitis is broad and includes sellar masses and pituitary thickening[51–53]. Distinguishing hypophysitis from macroadenoma is a common clinical concern. Intense enhancement of the pituitary is highly suggestive of hypophysitis. A 2009 study[40] created a score to help guide diagnosis. An asymmetrical increase in size, weak and heterogeneous enhancement, cavernous extension, erosion of the sellar floor, deviation of the stalk, and identification of a healthy portion of the pituitary gland should favour the hypothesis of an adenoma. Extrapituitary imaging features are also important for diagnosis, such as associated parenchymal or meningeal lesions and

extracranial lesions (head and neck or systemic). Finally, the temporal progression towards atrophy favours a diagnosis of hypophysitis over other aetiologies such as pituitary metastasis (Fig. 4). Of note, apart from hypophysitis, several pituitary disorders can cause hypopituitarism during pregnancy such as Sheehan syndrome and non-functioning adenoma[54].

Although haemochromatosis has been postulated as a potential cause of secondary hypophysitis, iron deposition in the pituitary gland typically occurs without associated inflammatory changes. Therefore, pituitary haemochromatosis is more appropriately considered a differential diagnosis rather than a distinct subtype of hypophysitis. Serum levels of ferritin should be systematically measured during the diagnostic work-up of hypophysitis, particularly in patients with gonadotroph deficiency[55,56].

Pituitary biopsy: its role and limitations in diagnosis

In this section, we differentiate between biopsies that are performed due to diagnostic uncertainty (non-resection biopsy) and biopsies that are performed during the course of surgery aimed to be curative (this type is discussed in detailed in the section 'Management and outcomes'). Fewer than 50 cases of non-resection biopsy have been reported in the literature. Despite its diagnostic value, the risks associated with all types of biopsy must be carefully considered, mainly because of complications such as pituitary hormone deficiency or AVP deficiency, which occur in approximately 14% of patients undergoing biopsy[57], as well as the risks associated with transsphenoidal surgery. In our clinical experience, biopsies or partial resections of anterior pituitary lesions appear to have a lower risk of endocrine deficiency and provide more material, resulting in more informative biopsies compared with stalk biopsies. As a consequence, biopsies should probably be limited to patients with an uncertain diagnosis and severe hypophysitis. It is important to note that the therapeutic management will probably remain the same with or without a biopsy, because the treatment strategy is only marginally influenced by the underlying cause of the hypophysitis.

Aetiological classification and diagnosis

Primary hypophysitis

Primary hypophysitis is a diagnosis of exclusion. Notably, hypophysitis can precede other clinical manifestations of an underlying systemic disease by several years, potentially leading to a misclassification as primary hypophysitis in the early stages[6]. Patients with primary hypophysitis are difficult to describe based on existing literature. Indeed, many studies have either mixed the aetiological subtypes or did not search for a secondary cause. We only discuss studies in which at least a minimal evaluation was performed to rule out

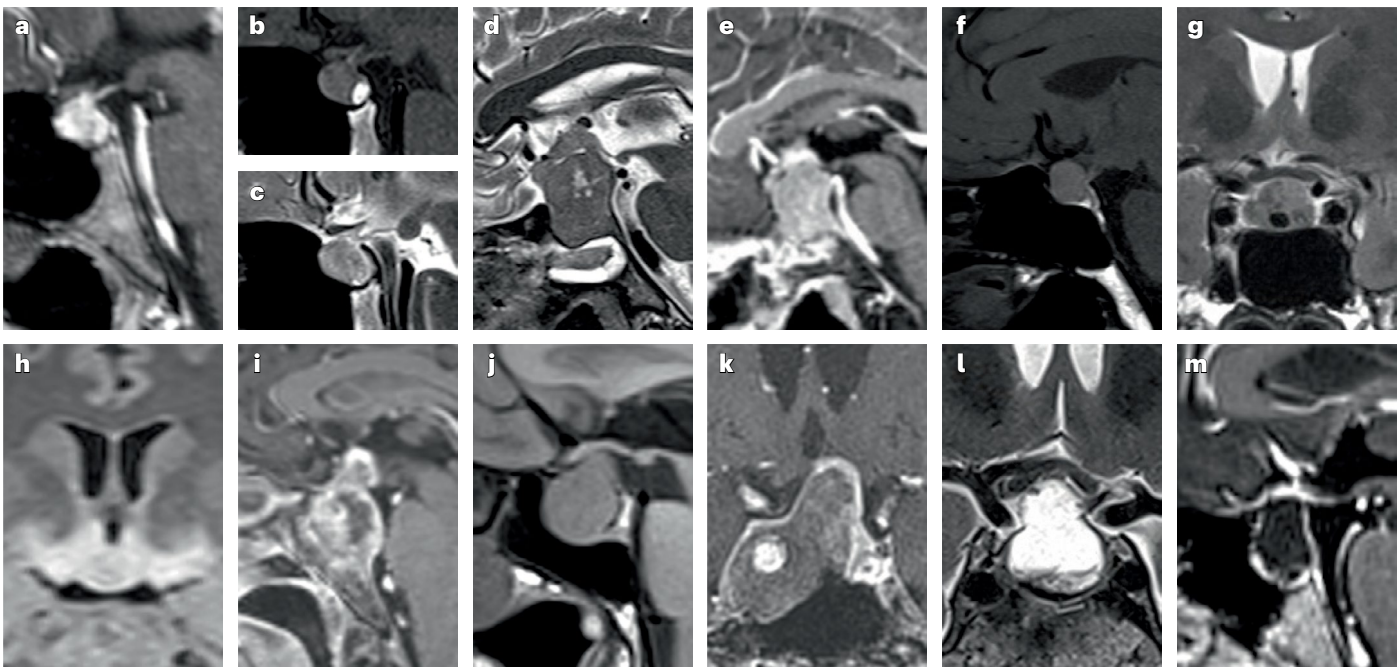

Fig. 4 | Differential diagnosis. Pituitary hyperplasia in a 23-year-old woman with headache (parts **a**–**c**) shows a size within normal limits for age, an enlarged homogeneously enhancing pituitary gland with a convex superior margin on the sagittal post-contrast T1-W image (part **a**), and a normal signal on the sagittal T1-W image (part **b**) and the T2-W image (part **c**). Germinoma of the central nervous system in a 20-year-old man (parts **d** and **e**) appears as a sellar and suprasellar heterogeneous mass on the coronal T2-W image (part **d**) and the sagittal post-contrast T1-W image (part **e**). Rathke cyst in a 53-year-old woman (parts **f** and **g**) appears as a hyperintense suprahypophyseal cystic lesion on the T1-W image (part **f**) with a hypointense nodule within the cyst on the T2-W image (part **g**). Pituitary metastasis in a 59-year-old man with lung cancer (parts **h** and **i**) shows extensive suprasellar parenchymal oedema on the coronal fluid-attenuated inversion recovery (FLAIR) image (part **h**) with a sellar necrotic lesion eroding the sphenoid bone on the sagittal post-contrast T1-W image (part **i**). Pituitary macroadenoma in a 57-year-old woman (parts **j** and **k**) shows as a persistent bright spot of the post-pituitary gland on the sagittal T1-W image (part **j**), asymmetrical enlargement of the pituitary gland with suprasellar extension, right cavernous invasion and depression of the right sellar floor, and persistence of a displaced layer of healthy pituitary gland at the periphery of the lesion on the coronal post-contrast T1-W image (part **k**). Craniopharyngioma in a 40-year-old man (parts **l** and **m**) appears as a sellar and suprasellar cystic lesion on the coronal T2-W image (part **l**) with peripheral enhancement on the sagittal post-contrast T1-W image (part **m**).

secondary hypophysitis[5,6,28,58–60]. A history of autoimmune disease is frequently reported in patients with primary hypophysitis (15–40% of patients)[5,6,28,58–60].

Pregnancy-related hypophysitis

Pregnancy-related hypophysitis was previously considered the most common form of the disease[61], but more recent studies published since 2015 have disproved this[58,59]. To be classified as pregnancy-related, hypophysitis must occur during or within 1 year of the start of pregnancy. It most commonly develops during the peripartum period, defined as the seventh to the ninth month of gestation and the 2 months following delivery[5]. A 2023 comparative study[5] analysed clinical, biological and MRI characteristics of pregnancy-related versus primary hypophysitis. In this study, patients with pregnancy-related hypophysitis more frequently presented with chiasmal syndrome (50% of patients), particularly when onset occurred during pregnancy, and showed similar rates of headache and oculomotor nerve involvement. Corticotroph deficiency was the most common dysfunction (71%), followed by thyrotroph and gonadotroph deficiencies (approximately 60%). AVP deficiency was notably rarer, affecting only 12% of women with pregnancy-related hypophysitis. MRI findings typically revealed a slightly thickened pituitary stalk and predominant intrasellar involvement, with a possible pseudo-adenoma-like appearance. Minor clinical differences were observed between women with pregnancy-related hypophysitis arising during pregnancy and those with hypophysitis arising in the postpartum period: chiasmal syndrome was more prevalent during pregnancy (64% of patients), whereas other clinical, hormonal and radiological features were largely similar. Interestingly, a history of autoimmune disease was reported in 22% of patients with pregnancy-associated hypophysitis, primarily thyroid autoimmunity[5].

Systemic diseases

To support the investigation of secondary hypophysitis caused by systemic diseases, a summary of the most common subtypes is provided in Table 1. This table also outlines the typical extrapituitary organ involvement associated with each condition, along with the relevant clinical and paraclinical methods used to assess such involvement.

Sarcoidosis. Although the prevalence of pituitary sarcoidosis is unknown, it is estimated to be less than 10% among individuals with neurosarcoidosis[50,62–64] and 1% among those with intrasellar lesions[65]. However, the prevalence of pituitary sarcoidosis is probably underestimated because it is not often looked for[66]. Few studies have included patients presenting with pituitary sarcoidosis[6,7,67–72]. Pituitary sarcoidosis can affect all pituitary functions but appears to cause mainly gonadotroph deficiency (75–87.5% of patients), followed by thyrotroph deficiency (40–65%), corticotroph deficiency (33–36%) and AVP deficiency (25–50%). Polydipsia and polyuria without AVP deficiency can also be found due to dysregulation of the hypothalamic thirst centre in hypothalamitis[73]. Hyperprolactinaemia has been reported in 30–77% of patients with sarcoidosis. On MRI, 50–64% of patients show infiltration of the pituitary stalk, and 34–58% show pituitary hyperplasia. Hypothalamic infiltration has been reported in 33–53% of patients. Pituitary sarcoidosis can be isolated[7,72], but is more commonly associated with multisystem sarcoidosis. Among the various manifestations, neurosarcoidosis appears to predispose most strongly to hypophysitis[6,7,67–72]. All patients with hypophysitis should therefore be investigated for the presence of sarcoidosis[6,11,74,75] (Table 1).

L-group histiocytosis. Histiocytoses are rare entities characterized by the accumulation of cells derived from dendritic cells or macrophages. The L-group histiocytoses share similar clonal mutations and clinical complications and notably include Langerhans cell histiocytosis (LCH) and Erdheim–Chester disease (ECD)[12]. Both are characterized by tissue infiltration of specific histiocytes ('LCH' or 'non-LCH'). A biopsy should be performed whenever possible, targeting the most accessible site or the site with the lowest risk of complications. These biopsies often reveal *BRAF*^{V600E} or MAPK–ERK pathway mutations[8,76,77]. Group L histiocytoses are known for their pituitary deficiencies (hypothalamic involvement is also possible), mainly leading to AVP deficiency. Pituitary inflammation can precede the diagnosis of histiocytosis by years[9,78,79]. ^{18}F-Fluorodeoxyglucose PET–CT is the most sensitive technique for detecting bone involvement. The rates of pituitary deficiency, including AVP deficiency are highly variable (5–55% in LCH versus 25–48% in ECD) and cannot be considered good aetiological markers[8,54,77,80–83]. The same is true for pituitary MRI, which might show infiltration of the pituitary stalk (20–71% in LCH versus 3–35% in ECD) or pituitary hyperplasia (0–35% in LCH versus 14% in ECD)[6,8,9,54,81,82]. Other symptoms might be seen and can help to differentiate the two entities: lytic bone lesions, and pulmonary, neurological, hepatic and splenic and skin involvement are seen in LCH[76] (Table 1). Bone involvement is seen in >80% of individuals with ECD and can be associated with neurological, pulmonary, aortic, retroperitoneal or skin involvement, and right atrial pseudotumour[77] (Table 1).

IgG4-related disease. IgG4-related hypophysitis is a chronic fibro-inflammatory disease characterized by lymphoplasmacytic infiltration. Diagnostic criteria for this condition were proposed in 2011 (refs. 84,85). Two literature reviews have described this specific entity[10,86] and report that the median age is 55 years (62 years in men versus 38 years in women). Headache was found to be present in 30% of patients, and visual pathway defects were seen in 16–20% of patients. At least one pituitary deficiency was observed in 75–78% of patients. AVP deficiency was the most common type, reported in 70–75% of all patients with IgG4-related hypophysitis, followed by gonadotroph deficiency. Other typical organ involvement seen in IgG4-related disease, such as pancreatic, salivary and lacrimal gland, chest, kidney or retroperitoneal involvement or lymphadenopathy should be searched for in the diagnosis[84,87–89] (Table 1).

COVID-19. Despite the widespread prevalence of COVID-19 and COVID vaccination, hypophysitis is a rare complication of this infection. To date, more than 770 million COVID-19 cases have been reported (WHO COVID-19 dashboard), with 67% of the general population globally having received a complete primary series of a COVID-19 vaccine. Pituitary involvement after vaccination has been reported in 23 individuals, including nine with hypophysitis (six women, three men, median age 46 years)[90]. Among patients infected with SARS-CoV-2, hypophysitis has been reported in seven (four women, three men, median age 37 years)[91] with a heterogeneous presentation, not allowing any firm conclusion to be drawn.

Others. Of note, Sjögren's syndrome[92,93], ANCA vasculitis[94,95], tuberculosis[96,97] and syphilis[98,99] have all been reported to cause hypophysitis, but hypophysitis is less commonly found with these conditions than in the aforementioned diseases (Table 1). Hypophysitis could be caused by a bacterial, fungal or viral infection. Hypophysitis is very rarely (fewer than cases) caused by or associated with lupus, inflammatory bowel disease, or thyroid disease.

Table 1 | Secondary hypophysitis: clinical signs and symptoms, prevalence and additional tests, according to the underlying cause

Underlying cause	Clinical and imaging features	Prevalence (%)	Expected signs	Investigations	Diagnosis
All systemic disease	NA	NA	NA	Blood analysis: CBC, quantitative serum immunoglobulin tests (including IgG4), SPEP, calcium, ACE, ANCA, ferritin, creatininaemia, ANA (anti-SSa and anti-SSb), IGRA test, TPHA, fasting blood glucose[a] Chest–abdominal CT scan[a] Tuberculin skin test[a] Clinical examination for a systemic disease[a] Cerebral MRI[a]	NA
Sarcoidosis[11,74,75]	Pulmonary	90	Micronodules Fibrosis Lymphocyte alveolitis	Chest CT scan[a] Pulmonary function tests BAL	Pathology with granulomas (large 'epithelioid' histiocytes) and multinucleated giant cells or a combination of signs (clinical, biological and radiological)
	Liver	20–30	Hepatomegaly Cholestasis Portal hypertension	Echography and CT scan Liver function tests	
	Eye	10–30	Uveitis Retinopathy	Ophthalmologist examination[b] Dilated eye examination with slit lamp[b]	
	Peripheral lymphadenopathy	10–20	Mostly cervical or supraclavicular	Chest CT scan[a]	
	Skin	15	Various lesions	Skin examination	
	Spleen	~10	Splenomegaly	Echography and CT	
	Nervous system	5	Lymphocytic meningitis Facial nerve palsy Deficits Psychiatric manifestations	Cerebral MRI[a] CSF analysis (lumbar puncture)[b]	
	Heart	2–5	Branch block Arrhythmia	Electrocardiogram Cardiac ultrasonography Cardiac MRI ^{18}F-FDG PET–CT with cardiac acquisition	
	Others		Hypercalcaemia ↑ ACE Tuberculin anergy Polyclonal hypergammaglobulinaemia ↑ Creatininaemia	Blood analysis[a]: calcium, ACE, SPEP, creatininaemia Tuberculin skin test[a] Salivary gland biopsy[b] (ref. 134)	
Erdheim–Chester disease[77]	Bones	>80 (38% symptomatic)	Long-bone osteosclerosis	Plain radiography or CT scan ^{18}F-FDG PET–CT[c]	Clinical and radiological findings Pathology with histiocytes CD68^{+} CD163^{+} FXIIIa^{+} and CD1a^{-} Molecular analysis: *BRAF*^{V600E} or MAPK–ERK pathway mutation if atypical clinical presentation
	Kidney	~60	Fat infiltration around the kidneys ('hairy kidneys') Bilateral hydronephrosis	Abdominal CT scan[a]	
	Neurological	~50	Enhancing masses or high signal density Meningeal involvement Exophthalmos	Neurological examination to identify cerebellar and pyramidal syndromes Cerebral MRI[a]	
	Pulmonary	<50	Infiltration of the pleura and lung parenchyma with an interstitial lung disease-like pattern	Chest CT scan[a]	
	Aortic	~40	Coated aorta	Aortic CT scan	
	Heart	~30	Right atrium pseudotumour Infiltration of coronary arteries Pericardial disease	Cardiac ultrasonography Cardiac MRI	
	Retroperitoneal	~30	Retroperitoneal infiltration	Abdominal CT scan[a]	
	Skin	~20	Xanthelasma around the eyes Non-specific lesions	Skin examination[c]	

Table 1 (continued) | Secondary hypophysitis: clinical signs and symptoms, prevalence and additional tests, according to the underlying cause

Underlying cause	Clinical and imaging features	Prevalence (%)	Expected signs	Investigations	Diagnosis
Langerhans cell histiocytosis[8,76]	Pulmonary	40–50	Solid or cavitated nodules and thick-walled or thin-walled cysts	Chest CT scan[a]	Clinical and radiological findings Pathology with histiocytes $CD68^+$ $CD163^+$ $CD207^-$ and $CD1a^+$ Lesional histiocytes with grooved and elongated nuclei Intermixed eosinophils possible Molecular analysis: $BRAF^{V600E}$ (70% of cases) or RAS–RAF–MEK–ERK pathway mutation if atypical clinical presentation
	Bones	30–50	Opposite painful or swollen areas (osteolytic lesions)	Plain radiography if visible lesions If not: ^{18}F-FDG PET–CT[c] or 99m-technetium skeletal scintigraphy	
	Neurological	15–20	Brain parenchyma infiltration (cerebellum or brainstem)	Neurological examination to identify ataxia and dysarthria Cerebral MRI[a]	
	Liver and spleen	10–15	Hepatosplenomegaly and hepatic nodules	Echography and CT[c]	
	Skin	5–10	Erythematous petechial papules that can be erosive, predominating on the scalp and in folds	Skin examination[c]	
IgG4-related disease[84,87–89]	Pancreas and biliary tree	~19–65	Diffuse pancreas enlargement Cholangitis	Abdominal CT scan[a]	Pituitary pathology with mononuclear infiltration, rich in lymphocytes and plasma cells, with more than ten $IgG4^+$ cells per high-power field (IgG staining or CD138 staining) Or abnormal pituitary MRI with pathology of another organ or increased serum levels of IgG4 and response to glucocorticoids
	Salivary and/or lachrymal glands	~18–28	Involvement usually bilateral: lacrimal glands, major salivary glands (parotid, sublingual, submandibular)	Clinical examination	
	Lymphatic	~17–27	Lymphadenopathy	Chest–abdominal CT scan[a]^{18}F-FDG PET–CT	
	Chest	~15–18	Peribronchovascular and septal thickening Pulmonary or pleural infiltration and fibrosis	Chest CT scan[a] ^{18}F-FDG PET–CT	
	Kidney	~12–13	Renal pelvic wall thickening Low-density areas in renal cortices Hypocomplementaemia	Abdominal CT scan[a] Blood analysis: C3, C4	
	Retroperitoneal	~10–18	Retroperitoneal peri-aortitis or fibrosis	Abdominal CT scan[a] ^{18}F-FDG PET–CT	
	Others		↑ Serum IgG4 concentration Blood eosinophilia	Blood analysis: IgG4, CBC	
Other underlying causes					
ANCA vasculitis[94]	NA	NA	↑ PR3 or MPO-ANCA ↑ Serum creatininaemia Interstitial lung diseases Intra-alveolar haemorrhage	Blood analysis: ANCA, creatininaemia[a] Chest CT scan[a] Clinical examination to identify crusted rhinitis or sinusitis	Clinical, biological, and histological evidence
Sjögren syndrome[92]	NA	NA	↑ ANA ↑ Anti-SSA (80% of cases) ↑ Anti-SSB (50% of cases)	Blood analysis: ANA (anti-SSA/ro, anti-SSB/La)[a]	Clinical, biological, and histological evidence
Tuberculosis[97]	NA	NA	IGRA usually positive TST usually positive Abnormal chest CT scan	Chest CT scan[a] IGRA[a] TST[a] Clinical examination to identify fever and dyspnoea	Clinical, biological, bacteriological and histological evidence
Syphilis	NA	NA	TPHA positive	Blood analysis: TPHA[a] Skin examination	Clinical and biological evidence

ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; BAL, bronchoalveolar lavage; CBC, complete blood count; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; IGRA, interferon-γ release assays; MPO, myeloperoxidase; NA, not applicable; PR3, proteinase 3; SPEP, serum protein electrophoresis; TPHA, *Treponema pallidum* haemagglutination assay; TST, tuberculin skin test. [a]To be sought systematically in all patients with hypophysitis, unless in those with pregnancy-related hypophysitis. [b]In the presence of a gonadotroph deficiency[6]. [c]Any vasopressin deficiency, without headache, associated with an infiltration of the pituitary stalk.

Immune checkpoint inhibitors

ICIs, notably anti-CTLA4 (ipilimumab) and anti-PD1 or PDL1 therapies (such as nivolumab, pembrolizumab or atezolizumab), have revolutionized cancer treatment but are associated with immune-related endocrine adverse events, particularly hypophysitis[100]. The incidence of hypophysitis reaches as high as 20% with anti-CTLA4 therapies, is less with anti-PD1 or PDL1 therapies (0.2–6%), and is even up to 30–40% with combination regimens[101,102]. Onset is typically earlier with anti-CTLA4 therapy (2–3 months) than with anti-PD1 or PDL1 therapies (4–6 months)[103,104].

Studies published over the past 5 years underline distinct clinical and pathophysiological patterns in ICI-associated hypophysitis. Anti-CTLA4 hypophysitis involves T cell mediated pituitary inflammation leading to combined anterior pituitary deficiencies (ACTH, TSH, gonadotropins) and transient pituitary enlargement on MRI[105,106]. By contrast, anti-PD1-related or PDL1-related hypophysitis typically presents with isolated ACTH deficiency, often asymptomatic, with infrequent radiological abnormalities, highlighting the need for systematic screening[16,103,107,108]. Long-term data on anti-CTLA4, anti-PD1 or PDL1 therapies reveal frequent persistence of corticotroph deficiency, requiring lifelong replacement therapy, whereas the thyrotroph and gonadotroph axes can recover[102,109,110].

Paraneoplastic hypophysitis

Pit1 (*POU1F1*) is a late-acting pituitary-specific transcription factor involved in the final steps of GH-producing, TSH-producing and prolactin-producing pituitary cell differentiation. Anti-Pit1 antibodies were first described in a 2011 study in three patients with thymoma with TSH, GH and prolactin deficiencies[111]. The pathophysiological mechanism of paraneoplastic hypophysitis involves the ectopic expression of Pit1 in tumour tissue, leading to the activation of Pit1-reactive cytotoxic T cells[112] and the production of anti-Pit1 antibodies. These T cells, rather than the antibodies, subsequently target GH-producing, prolactin-producing and TSH-producing cells in the pituitary gland. To date, nine patients considered to have paraneoplastic hypophysitis have been reported[14], four with thymoma and five with various malignancies. All patients had GH and prolactin deficiency, and very low TSH levels. All patients showed a normal or slightly atrophic pituitary gland on MRI. Anti-Pit1 antibodies were detected in all but one patient who presented with Pit1-reactive T cells. Interestingly, these antibodies are not toxic to pituitary cells and should therefore be considered as markers rather than agents of paraneoplastic hypophysitis[113]. The condition could have a genetic predisposition, as all reported patients were from Japan with specific HLA features. Interestingly, anti-Pit1 hypophysitis has been reported in patients treated with ICIs. A 2025 Comment article hypothesized that ectopic Pit1 expression could be present in a number of patients with malignancies, and that ICI treatment might lead to a transition from a preclinical to a clinical form of hypophysitis[114].

Management and outcomes

Treatment approaches can be classified as disease-controlling therapies or substitutive treatments. Disease-controlling therapies aim to resolve hypophysitis by reducing or stopping intrapituitary inflammation, thereby alleviating or eliminating associated clinical and hormonal symptoms. By contrast, substitutive treatments are intended to compensate for hormone deficiencies resulting from hypopituitarism. Conservative management, involving no treatments other than substitutive treatments, can be considered for mild forms of the disease, or at the patient's request. Approaches to the management of hypophysitis in relation to aetiological subtype are summarized in Table 2. These treatment strategies are shared for informational purposes only. They reflect our clinical practice but are not based on sufficient evidence to be considered as formal recommendations. Therapeutic decisions should always be individualized and discussed within a multidisciplinary team.

Disease-controlling therapies

Glucocorticoids. There is a limited amount of data in the literature regarding the appropriate glucocorticoid dosage for treatment of hypophysitis. In this section we present advice based on our experience for the use of glucocorticoids in the management of hypophysitis.

For hypophysitis with chiasmal compression or oculomotor nerve palsy, high-dose intravenous glucocorticoids can be administered at 1 g/day for 3–5 days. In patients with clinical deterioration or lack of improvement, debulking surgery can be considered. This is usually followed by oral glucocorticoid therapy at 1 mg/kg/day, with a gradual tapering over at least 1 year.

In patients with hypophysitis with a mass effect but no visual involvement, oral glucocorticoid therapy can be initiated at 1 mg/kg/day, with a progressive tapering over a minimum of 1 year.

In patients with hypophysitis with substantial endocrine dysfunction, with or without severe headaches and who are otherwise in good general health with a life expectancy exceeding 20 years, a course of oral glucocorticoids can be considered for 6 to 12 months, starting at 0.5 to 1 mg/kg/day, depending on clinical severity and response.

The proposal for pulse therapy is based on an aggressive approach similar to that for the treatment of severe neurosarcoidosis[64]. By analogy with systemic autoimmune diseases such as necrotizing vasculitis, glucocorticoid tapering can follow previous established protocols: a 12-month taper according to the CORTAGE trial[115], or a 6-month taper following the low-dose regimen used in the PEXIVAS trial[116].

Immunosuppressive treatments. Prioritizing safety profile over demonstrated clinical efficacy, we propose a hierarchical treatment strategy, starting with mycophenolate mofetil (2 g/day, introduced gradually over several weeks) as the preferred first-line option. This treatment can be followed by azathioprine (1–2 mg/kg/day), rituximab (1 g on days 1 and 15, then 500 mg every 6 months), and finally infliximab (3–5 mg/kg every 8 weeks). Each of these immunosuppressive agents requires specific safety monitoring prior to initiation[117]. Their use in this context is off-label. Beyond safety concerns, the choice of immunosuppressant will also be guided by the underlying aetiology and (if applicable) the pregnancy plans of the patient (Fig. 5). Moreover, because rituximab and anti-TNF agents are given intravenously, adherence can be ensured more easily. The choice of immunosuppressive therapy — whether as monotherapy or in combination with glucocorticoids — should be tailored to the severity of the clinical presentation and discussed within a multidisciplinary team.

Surgery. Surgical resection (non-resection biopsy is not discussed in this section) via a transsphenoidal approach has a very limited role in the treatment of hypophysitis. Today, its use is limited to hypophysitis with visual impairment associated with an optic pathway mass effect on MRI and failure of glucocorticoid therapy. Hypophysitis usually appears as a greyish adherent tissue or can be creamy in colour. Surgery has been shown usually to improve the visual prognosis in these patients[118]. However, surgery might worsen pituitary function, especially when compared with glucocorticoids or watchful waiting without specific treatment[27]. By contrast, surgery rarely leads to severe non-endocrine complications[118].

Table 2 | Management of hypophysitis in relation to aetiological subtype

Treatment		Primary hypophysitis	Pregnancy-related hypophysitis		Secondary hypophysitis			
			Pregnancy-onset	Postpartum-onset	ICI-related[2]	Sarcoidosis	L-group histiocytosis[76,132]	IgG4-related disease[13]
Substitutive treatments		Suitable for pituitary deficiency						
Conservative treatment		Mild form with few symptoms						
Glucocorticoids	High-dose intravenous glucocorticoid at 1 g/day for 3 to 5 days followed by oral glucocorticoid therapy at 1 mg/kg/day, with a gradual taper over at least 1 year	If chiasmatic syndrome or damage to the oculomotor nerves If unsuccessful, discuss surgery or radiotherapy						
	Oral glucocorticoid therapy at 1 mg/kg/day, with a gradual taper over at least 1 year	Mass effect without chiasmatic syndrome			No	Yes	To be discussed	Yes
	Oral glucocorticoid therapy at 0.5 mg/kg/day, with a gradual taper over 6 months	Substantial endocrine dysfunction, with or without headaches			No	No		Yes (0.6 mg/kg/day)
Immunosuppressive treatments	Mycophenolate mofetil, 2 g/day, introduced gradually over several weeks	Possible	No	No	No	Possible, often in combination with glucocorticoid	No	Possible
	Azathioprine, 1–2 mg/kg/day	Possible	Possible	Possible	No	Possible, often in combination with glucocorticoid	No	Possible
	Rituximab, 1 g on days 1 and 15, then 500 mg every 6 months	Possible	No	No	No	No	No	Possible
	Infliximab, 3–5 mg/kg every 8 weeks	Possible	No	Possible	No	Possible, often in combination with glucocorticoid	No	No
	Methotrexate	Unreported	No	No	No	Possible, often in combination with glucocorticoid	No	Possible
Surgery		Failed glucocorticoid for the treatment of chiasmatic syndrome						
Radiotherapy		Failed surgery or contraindication to surgery						

Radiotherapy. Only scarce data have been published on the efficacy of radiotherapy for the treatment of hypophysitis, with limited follow-up[119]. A 2024 systematic literature review reported eight patients treated with focused radiation techniques (Gamma Knife radiosurgery of fractionated stereotactic radiotherapy), all of whom had their final glucocorticoid dose reduced. Three patients showed complete shrinkage of the mass, while the others showed stable or decreased volume on MRI. Pituitary deficiency was present before radiotherapy in seven patients, and one patient presented with panhypopituitarism after the procedure[120]. Radiotherapy could be an option in patients who have failed surgery and glucocorticoids, although the long-term efficacy and consequences are unknown.

Indications of disease-controlling therapies according to subtypes

Figure 5 summarizes the various treatment options according to the subtype of hypophysitis and the extent of clinical involvement (for example, visual impairment or the presence of a large sellar mass). The following sections review how these treatments have been documented in the literature.

Primary hypophysitis. There is no consensus on the role of glucocorticoids in the treatment of primary hypophysitis, but they are often used as a first-line treatment along with monitoring. According to a 2022 meta-analysis, glucocorticoid therapy is associated with a higher rate of partial or complete recovery of endogenous endocrine function in patients with primary or pregnancy-related hypophysitis compared with observation or surgery[57]. Glucocorticoids have been shown to improve visual impairment[57,121], relieve headaches[6,57], promote recovery of pituitary function[122] and prevent new deficits[57,122]. Doses range from 0.5 mg/kg/day (orally) to 1 g/day by intravenous injection[119]. Decreased dosage usually occurs within 3 months of initiation[121]. However, the optimal duration of treatment has not been established. A period longer than 3 months is recommended to prevent relapse[32]. A single clinical trial in 20 patients evaluated the effect of glucocorticoids in hypophysitis treated with 50 mg/day with a gradual tapering

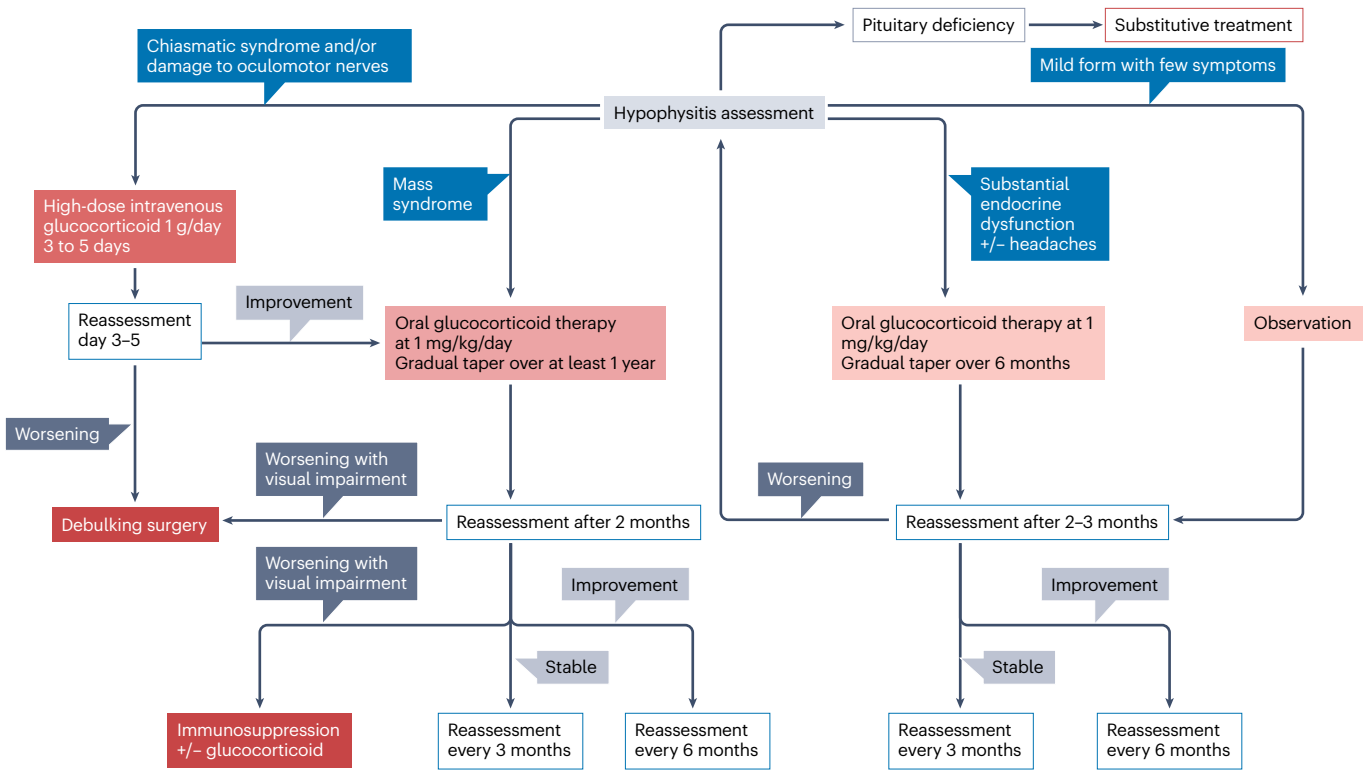

Fig. 5 | Management of hypophysitis. Proposed algorithm for the management of hypophysitis based on clinical, biological and MRI findings. Substitutive treatment and disease-controlling therapies with reassessment periods are proposed.

over 13 months[122]. An improved endocrine prognosis was observed, but patients experienced adverse effects. Literature reviews report adverse effects in about half of patients, emphasizing the need to monitor for these adverse effects and for iatrogenic adrenocorticotropic insufficiency after withdrawal[121,123–125].

Some immunosuppressive agents have been tried in the treatment of primary hypophysitis, often in combination with glucocorticoids[126] or when glucocorticoids were contraindicated or ineffective. These therapies include conventional immunosuppressive drugs such as azathioprine or mycophenolate mofetil, and biotherapeutics such as infliximab and rituximab. However, none of these has been evaluated in clinical trials for use in hypophysitis, with only case reports or small series available[127].

Pregnancy-related hypophysitis. Treatment has traditionally involved surgery or conservative management; more rarely, patients have been treated using glucocorticoids alone or in combination with surgery. However, the role of surgery has markedly declined over the past 15 years, with conservative approaches becoming increasingly favoured. Relapse has been reported in approximately 8% of patients, particularly in those managed with glucocorticoids[5]. Nevertheless, it is difficult to draw firm conclusions about the efficacy of glucocorticoids from these observations alone, given that the dosage and duration of glucocorticoid therapy use varies considerably between patients[5].

Secondary hypophysitis. The specific treatment of secondary hypophysitis depends on its underlying cause. Recovery of pituitary function might be observed but is inconsistent. AVP deficiency does not usually recover, regardless of the underlying cause[6–10].

ICI-related hypophysitis: Current international guidelines recommend continuing ICI treatment, initiating hormone replacement, especially hydrocortisone if needed in an emergency, and reserving high-dose corticosteroids for severe symptoms[2,4,16,128]. To date, no treatment has been shown to reverse immune-induced endocrine damage[2]. Hormone replacement therapy tailored to the specific deficiencies remains the mainstay of treatment[2]. Regular endocrine monitoring and long-term multidisciplinary follow-up, including patient education, are essential[16].

Sarcoidosis: Patients with pituitary sarcoidosis might show normalization of their prolactin levels and sometimes recover gonadotroph function[7,68,69]. There are no guidelines for the treatment of hypophysitis in sarcoidosis[75]. Treatment of neurosarcoidosis usually requires high doses of glucocorticoids, starting with an intravenous injection (500–1,000 mg per day) for a few days followed by 1 mg/kg/day, with gradual tapering over several months. This treatment regimen is often combined with other immunosuppressive drugs, including methotrexate, infliximab, mycophenolate mofetil, azathioprine or cyclophosphamide[64]. These treatments typically relieve patients' headaches[6].

L-group histiocytosis: AVP deficiency in histiocytosis typically shows little or no recovery[8]. Treatment of group L-histiocytosis depends on the subtype and extent of the disease. The efficacy of glucocorticoids is debatable. Apart from conventional therapies (chemotherapy, IFNα, cladribine and anakinra), targeted therapies such as

BRAF and MEK inhibitors have shown promising results in patients with systemic involvement[129,130]. Very brief reports of recovery from endocrine involvement in adults under these new therapies have been published[131]. Treatment options should be discussed with specialists, taking into account the clinical findings, disease progression, and the specific mutation identified[76,132].

IgG4 related disease: Lymphoproliferative lesions associated with IgG4-related disease typically show a good response to glucocorticoids (0.6 mg/kg)[13]. Immunosuppressive agents such as rituximab, azathioprine, methotrexate and mycophenolate mofetil have also demonstrated efficacy. These immunosuppressive therapies are particularly favoured in patients in whom glucocorticoids are contraindicated. A 2025 Review proposed a therapeutic algorithm to guide treatment selection[13].

Paraneoplastic hypophysitis. To date, only a few cases of paraneoplastic hypophysitis have been described. It seems acceptable to treat the underlying cancer without specific therapeutic interventions for the hypophysitis itself. Glucocorticoid treatment might work, but there is not enough evidence to consider it in a systematic therapeutic approach.

Hypopituitarism and substitutive treatments

The initial hormonal evaluation for pituitary deficiencies (discussed previously) guides replacement therapy, which is the same regardless of the aetiology of hypopituitarism[36]. However, depending on the aetiology, and possibly on the type of treatment (although this point remains controversial for some aetiologies)[122], hormonal evaluation can be performed every 6–12 months to check for recovery. Recovery remains uncommon. In the case of ACTH deficiency or AVP deficiency, education of the patient and the patient's family regarding sick day rules is mandatory[133].

Conclusions

Hypophysitis, often diagnosed according to different criteria, is a heterogeneous disease that includes several entities. We propose that a revised classification based on clinical, biological and imaging characteristics could be worthwhile to avoid misdiagnosis and non-optimal management of primary pregnancy-related and secondary hypophysitis. In parallel, large international epidemiological studies should be performed to better characterize the different subtypes of hypophysitis. In patients with hypophysitis, the possibility of an underlying systemic disease should indeed be systematically investigated to avoid a false diagnosis of 'primary' hypophysitis. Collaborative studies should also help tailor the treatment. In our current state of knowledge, the systematic use of glucocorticoids should be discussed in all cases of primary or pregnancy-related hypophysitis and in patients with visual impairment (before surgical intervention). The optimal duration and dose are yet to be defined and should be considered as main priorities for future research. The complexity of the disease makes multidisciplinary management of these patients essential.

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References

1. Goudie, R. B. & Pinkerton, P. H. Anterior hypophysitis and Hashimoto's disease in a young woman. *J. Pathol. Bacteriol.* **83**, 584–585 (1962).
2. Husebye, E. S. et al. Endocrine-related adverse conditions in patients receiving immune checkpoint inhibition: an ESE clinical practice guideline. *Eur. J. Endocrinol.* **187**, G1–G21 (2022). **These are the latest recommendations for the treatment of immune checkpoint inhibitor-induced hypophysitis.**
3. Wright, J. J., Powers, A. C. & Johnson, D. B. Endocrine toxicities of immune checkpoint inhibitors. *Nat. Rev. Endocrinol.* **17**, 389–399 (2021).
4. Schneider, B. J. et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J. Clin. Oncol.* **39**, 4073–4126 (2021).
5. Honegger, J., Giese, S., Nasi-Kordhishti, I. & Donegan, D. M. Pregnancy-related hypophysitis revisited. *Eur. J. Endocrinol.* **188**, R1–R12 (2023). **This is the largest study comparing hypophysitis related and unrelated to pregnancy.**
6. Miquel, L. et al. Deciphering the presentation and etiologies of hypophysitis highlights the need for repeated systematical investigation. *J. Clin. Endocrinol. Metab.* **110**, e1767–e1775 (2024).
7. Langrand, C. et al. Hypothalamo-pituitary sarcoidosis: a multicenter study of 24 patients. *QJM* **105**, 981–995 (2012).
8. Sagna, Y. et al. Endocrine manifestations in a cohort of 63 adulthood and childhood onset patients with Langehans cell histiocytosis. *Eur. J. Endocrinol.* **181**, 275–285 (2019). **With 40 adults and 23 children, this is the largest retrospective cohort with pituitary involvement in patients with Langerhans cell histiocytosis.**
9. Courtillot, C. et al. Endocrine manifestations in a monocentric cohort of 64 patients with erdheim-chester disease. *J. Clin. Endocrinol. Metab.* **101**, 305–313 (2016). **This article represents the largest endocrine retrospective cohort of patients with Erdheim–Chester disease.**
10. Amirbaigloo, A., Esfahanian, F., Mouodi, M., Rakhshani, N. & Zeinalizadeh, M. IgG4-related hypophysitis. *Endocrine* **73**, 270–291 (2021).
11. Crouser, E. D. et al. Diagnosis and detection of sarcoidosis. An official American Thoracic Society clinical practice guideline. *Am. J. Respir. Crit. Care Med.* **201**, e26–e51 (2020).
12. Emile, J.-F. et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood* **127**, 2672–2681 (2016).
13. Peyronel, F. et al. IgG4-related disease and other fibro-inflammatory conditions. *Nat. Rev. Rheumatol.* **21**, 275–290 (2025).
14. Urai, S. et al. Clinical features of anti-pituitary-specific transcription factor-1 (PIT-1) hypophysitis: a new aspect of paraneoplastic autoimmune condition. *Eur. J. Endocrinol.* **190**, K1–K7 (2024).
15. Langlois, F., Varlamov, E. V. & Fleseriu, M. Hypophysitis, the growing spectrum of a rare pituitary disease. *J. Clin. Endocrinol. Metab.* **107**, 10–28 (2021). **This article reviews the different types and causes of hypophysitis, major published cohort series and diagnostic and therapeutic approaches.**
16. Castinetti, F. et al. French Endocrine Society guidance on endocrine side effects of immunotherapy. *Endocr. Relat. Cancer* **26**, G1–G18 (2018).
17. Vardarli, I. et al. Risk and incidence of endocrine immune-related adverse effects under checkpoint inhibitor mono- or combination therapy in solid tumors: a meta-analysis of randomized controlled trials. *J. Clin. Endocrinol. Metab.* **109**, 1132–1144 (2024).
18. Caturegli, P. et al. Autoimmune hypophysitis. *Endocr. Rev.* **26**, 599–614 (2005).
19. Howlett, T. A., Levy, M. J. & Robertson, I. J. How reliably can autoimmune hypophysitis be diagnosed without pituitary biopsy. *Clin. Endocrinol.* **73**, 18–21 (2010).
20. Buxton, N. & Robertson, I. Lymphocytic and granulocytic hypophysitis: a single centre experience. *Br. J. Neurosurg.* **15**, 242–246 (2001).
21. Imga, N. N., Yildirim, A. E., Baser, O. O. & Berker, D. Clinical and hormonal characteristics of patients with different types of hypophysitis: a single-center experience. *Arch. Endocrinol. Metab.* **63**, 47–52 (2019).
22. Honegger, J. et al. Lymphocytic and granulomatous hypophysitis: experience with nine cases. *Neurosurgery* **40**, 713–723 (1997).
23. Leung, G. K. K., Lopes, M.-B. S., Thorner, M. O., Vance, M. L. & Laws, E. R. Primary hypophysitis: a single-center experience in 16 cases. *J. Neurosurg.* **101**, 262–271 (2004).
24. Sautner, D., Saeger, W., Lüdecke, D. K., Jansen, V. & Puchner, M. J. Hypophysitis in surgical and autoptical specimens. *Acta Neuropathol.* **90**, 637–644 (1995).
25. Gutenberg, A., Buslei, R., Fahlbusch, R., Buchfelder, M. & Brück, W. Immunopathology of primary hypophysitis: implications for pathogenesis. *Am. J. Surg. Pathol.* **29**, 329–338 (2005).
26. Tashiro, T. et al. Spectrum of different types of hypophysitis: a clinicopathologic study of hypophysitis in 31 cases. *Endocr. Pathol.* **13**, 183–195 (2002).
27. Hacioglu, A. et al. Evaluation and follow-up of patients diagnosed with hypophysitis: a cohort study. *Eur. J. Endocrinol.* **191**, 312–322 (2024).
28. Amereller, F., Küppers, A.-M., Schilbach, K., Schopohl, J. & Störmann, S. Clinical characteristics of primary hypophysitis — a single-centre series of 60 cases. *Exp. Clin. Endocrinol. Diabetes* **129**, 234–240 (2021).
29. Ju, J.-S., Cui, T., Zhao, J., Chen, J.-L. & Ju, H.-B. Clinical presentation and magnetic resonance imaging characteristics of lymphocytic hypophysitis: a systematic review with meta-analysis. *Arch. Med. Sci.* **19**, 976–986 (2023).
30. Imber, B. S., Lee, H. S., Kunwar, S., Blevins, L. S. & Aghi, M. K. Hypophysitis: a single-center case series. *Pituitary* **18**, 630–641 (2015).
31. Korkmaz, O. P. et al. Primary hypophysitis: experience of a single tertiary center. *Exp. Clin. Endocrinol. Diabetes* **129**, 14–21 (2021).
32. Wang, S. et al. Primary lymphocytic hypophysitis: clinical characteristics and treatment of 50 cases in a single centre in China over 18 years. *Clin. Endocrinol.* **87**, 177–184 (2017).
33. Zhu, Q. et al. Clinical features, magnetic resonance imaging, and treatment experience of 20 patients with lymphocytic hypophysitis in a single center. *World Neurosurg.* **127**, e22–e29 (2019).
34. Atkins, P. & Ur, E. Primary and ipilimumab-induced hypophysitis: a single-center case series. *Endocr. Res.* **45**, 246–253 (2020).

35. Türe, U. et al. Hypothalamitis: a novel autoimmune endocrine disease. a literature review and case report. *J. Clin. Endocrinol. Metab.* **106**, e415–e429 (2021).
36. Fleseriu, M., Christ-Crain, M., Langlois, F., Gadelha, M. & Melmed, S. Hypopituitarism. *Lancet* **403**, 2632–2648 (2024).
37. Arlien-Søborg, M. C., Karavitaki, N. & Jorgensen, J. O. L. Consensus and controversies about diagnosing GH deficiency: a Delphi survey by the GH Research Society. *Pituitary* **28**, 57 (2025).
38. Bonneville, J.-F., Bonneville, F., Cattin, F. & Nagi, S. *MRI of the Pituitary Gland* (Springer, 2016).
39. Caranci, F. et al. Imaging findings in hypophysitis: a review. *Radiol. Med.* **125**, 319–328 (2020).
40. Gutenberg, A., Larsen, J., Lupi, I., Rohde, V. & Caturegli, P. A radiologic score to distinguish autoimmune hypophysitis from nonsecreting pituitary adenoma preoperatively. *AJNR Am. J. Neuroradiol.* **30**, 1766–1772 (2009).
This article summarizes the radiological features of hypophysitis and proposes a radiological score to differentiate adenoma from hypophysitis. This score is useful in adenoma-like hypophysitis.
41. Kurokawa, R. et al. Neuroimaging of hypophysitis: etiologies and imaging mimics. *Jpn. J. Radiol.* **41**, 911–927 (2023).
42. Nakata, Y. et al. Parasellar T2 dark sign on MR imaging in patients with lymphocytic hypophysitis. *AJNR Am. J. Neuroradiol.* **31**, 1944–1950 (2010).
43. Bathla, G., Singh, A. K., Policeni, B., Agarwal, A. & Case, B. Imaging of neurosarcoidosis: common, uncommon, and rare. *Clin. Radiol.* **71**, 96–106 (2016).
44. Smith, J. K., Matheus, M. G. & Castillo, M. Imaging manifestations of neurosarcoidosis. *Am. J. Roentgenol.* **182**, 289–295 (2004).
45. Zhu, J. et al. Xanthomatous hypophysitis: a case report and comprehensive literature review. *Front. Endocrinol.* **12**, 735655 (2021).
46. Duan, K. et al. Xanthomatous hypophysitis is associated with ruptured Rathke's cleft cyst. *Endocr. Pathol.* **28**, 83–90 (2017).
47. Temizkan, S. & Kelestimur, F. A clinical and pathophysiological approach to traumatic brain injury-induced pituitary dysfunction. *Pituitary* **22**, 220–228 (2019).
48. De Bellis, A. et al. Detection of antipituitary and antihypothalamus antibodies to investigate the role of pituitary or hypothalamic autoimmunity in patients with selective idiopathic hypopituitarism. *Clin. Endocrinol.* **75**, 361–366 (2011).
49. Iwama, S. et al. Rabphilin-3A as a targeted autoantigen in lymphocytic infundibulo-neurohypophysitis. *J. Clin. Endocrinol. Metab.* **100**, E946–E954 (2015).
50. Ozawa, Y. & Shishiba, Y. Recovery from lymphocytic hypophysitis associated with painless thyroiditis: clinical implications of circulating antipituitary antibodies. *Acta Endocrinol. (Copenh.)* **128**, 493–498 (1993).
51. Shih, R. Y., Schroeder, J. W. & Koeller, K. K. Primary tumors of the pituitary gland: radiologic-pathologic correlation. *Radiographics* **41**, 2029–2046 (2021).
52. Huang, J., Sarma, A., Harmsen, H. & Pruthi, S. Systematic approach to evaluating sellar and suprasellar lesions in pediatric patients. *Radiographics* **42**, E214–E215 (2022).
53. Lubomirsky, B. et al. Sellar, suprasellar, and parasellar masses: imaging features and neurosurgical approaches. *Neuroradiol. J.* **35**, 269–283 (2022).
54. Makras, P. et al. Evolving radiological features of hypothalamo-pituitary lesions in adult patients with Langerhans cell histiocytosis (LCH). *Neuroradiology* **48**, 37–44 (2006).
55. Prodam, F., Caputo, M., Mele, C., Marzullo, P. & Aimaretti, G. Insights into non-classic and emerging causes of hypopituitarism. *Nat. Rev. Endocrinol.* **17**, 114–129 (2021).
56. Pelusi, C., Gasparini, D. I., Bianchi, N. & Pasquali, R. Endocrine dysfunction in hereditary hemochromatosis. *J. Endocrinol. Invest.* **39**, 837–847 (2016).
57. Donegan, D. et al. Outcomes of initial management strategies in patients with autoimmune lymphocytic hypophysitis: a systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* **107**, 1170–1190 (2022).
Diagnostic criteria for IgG4-related hypophysitis are proposed in this study.
58. Honegger, J. et al. Diagnosis of primary hypophysitis in Germany. *J. Clin. Endocrinol. Metab.* **100**, 3841–3849 (2015).
59. Khare, S. et al. Primary (autoimmune) hypophysitis: a single centre experience. *Pituitary* **18**, 16–22 (2015).
60. Oguz, S. H. et al. Clinical characteristics, management, and treatment outcomes of primary hypophysitis: a monocentric cohort. *Horm. Metab. Res.* **52**, 220–227 (2020).
61. Cosman, F., Post, K. D., Holub, D. A. & Wardlaw, S. L. Lymphocytic hypophysitis. report of 3 new cases and review of the literature. *Medicine* **68**, 240–256 (1989).
62. Ramos-Casals, M. et al. Clinical characterization and outcomes of 85 patients with neurosarcoidosis. *Sci. Rep.* **11**, 13735 (2021).
63. Leonhard, S. E. et al. Neurosarcoidosis in a tertiary referral center: a cross-sectional cohort study. *Medicine* **95**, e3277 (2016).
64. Bradshaw, M. J., Pawate, S., Koth, L. L., Cho, T. A. & Gelfand, J. M. Neurosarcoidosis: pathophysiology, diagnosis, and treatment. *Neurol. Neuroimmunol. Neuroinflammation* **8**, e1084 (2021).
65. Freda, P. U. & Post, K. D. Differential diagnosis of sellar masses. *Endocrinol. Metab. Clin. North. Am.* **28**, 81–117 (1999).
66. Bihan, H. et al. Sarcoïdose : l'atteinte des hormones à dépendance antéhypophysaire est insuffisamment diagnostiquée [French]. *Presse Med* **41**, e524–e529 (2012).
67. Bullmann, C. et al. Five cases with central diabetes insipidus and hypogonadism as first presentation of neurosarcoidosis. *Eur. J. Endocrinol.* **142**, 365–372 (2000).
68. Bihan, H. et al. Sarcoidosis: clinical, hormonal, and magnetic resonance imaging (MRI) manifestations of hypothalamic-pituitary disease in 9 patients and review of the literature. *Medicine* **86**, 259–268 (2007).
69. Ramos, N. et al. Sarcoïdose hypothalamo-hypophysaire: étude multicentrique de 32 patients [French]. *Rev. Med. Interne* **39**, A92 (2018).
70. Tabuena, R. P. et al. Diabetes insipidus from neurosarcoidosis: long-term follow-up for more than eight years. *Intern. Med.* **43**, 960–966 (2004).
71. Martin-Grace, J., Murialdo, G. & Tamagno, G. Hypothalamic–pituitary alterations in patients with neurosarcoidosis. *EMJ Neurol.* **3**, 51–56 (2015).
72. Anthony, J., Esper, G. J. & Ioachimescu, A. Hypothalamic-pituitary sarcoidosis with vision loss and hypopituitarism: case series and literature review. *Pituitary* **19**, 19–29 (2016).
73. Stuart, C. A., Neelon, F. A. & Lebovitz, H. E. Disordered control of thirst in hypothalamic-pituitary sarcoidosis. *N. Engl. J. Med.* **303**, 1078–1082 (1980).
74. Valeyre, D. et al. Sarcoidosis. *Lancet* **383**, 1155–1167 (2014).
75. Baughman, R. P. et al. ERS clinical practice guidelines on treatment of sarcoidosis. *Eur. Respir. J.* **58**, 2004079 (2021).
76. Goyal, G. et al. International expert consensus recommendations for the diagnosis and treatment of Langerhans cell histiocytosis in adults. *Blood* **139**, 2601–2621 (2022).
77. Haroche, J., Cohen-Aubart, F. & Amoura, Z. Erdheim–Chester disease. *Blood* **135**, 1311–1318 (2020).
78. Cavalli, G. et al. The multifaceted clinical presentations and manifestations of Erdheim–Chester disease: comprehensive review of the literature and of 10 new cases. *Ann. Rheum. Dis.* **72**, 1691–1695 (2013).
79. Kaltsas, G. A. et al. Hypothalamo-pituitary abnormalities in adult patients with Langerhans cell histiocytosis: clinical, endocrinological, and radiological features and response to treatment. *J. Clin. Endocrinol. Metab.* **85**, 1370–1376 (2000).
80. Montefusco, L. et al. Endocrine and metabolic assessment in adults with Langerhans cell histiocytosis. *Eur. J. Intern. Med.* **51**, 61–67 (2018).
81. Makras, P., Alexandraki, K. I., Chrousos, G. P., Grossman, A. B. & Kaltsas, G. A. Endocrine manifestations in Langerhans cell histiocytosis. *Trends Endocrinol. Metab.* **18**, 252–257 (2007).
82. Estrada-Veras, J. I. et al. The clinical spectrum of Erdheim–Chester disease: an observational cohort study. *Blood Adv.* **1**, 357–366 (2017).
83. Cives, M. et al. Erdheim–Chester disease: a systematic review. *Crit. Rev. Oncol. Hematol.* **95**, 1–11 (2015).
84. Leporati, P., Landek-Salgado, M. A., Lupi, I., Chiovato, L. & Caturegli, P. IgG4-related hypophysitis: a new addition to the hypophysitis spectrum. *J. Clin. Endocrinol. Metab.* **96**, 1971–1980 (2011).
This article provides insights into IgG4-related hypophysitis, diagnosis and management.
85. Bando, H. et al. The prevalence of IgG4-related hypophysitis in 170 consecutive patients with hypopituitarism and/or central diabetes insipidus and review of the literature. *Eur. J. Endocrinol.* **170**, 161–172 (2014).
86. Lojou, M., Bonneville, J. F., Ebbo, M., Schleinitz, N. & Castinetti, F. IgG4 hypophysitis: diagnosis and management. *Presse Med.* **49**, 104016 (2020).
87. Wallace, Z. S. et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Arthritis Rheumatol.* **72**, 7–19 (2020).
88. Wallace, Z. S. et al. IgG4-related disease: baseline clinical and laboratory features in 125 patients with biopsy-proven disease. *Arthritis Rheumatol.* **67**, 2466–2475 (2015).
89. Sekiguchi, H. et al. IgG4-related disease: retrospective analysis of one hundred sixty-six patients. *Arthritis Rheumatol.* **68**, 2290–2299 (2016).
90. Verrienti, M., Picciola, V. M., Ambrosio, M. R. & Zatelli, M. C. Pituitary and COVID-19 vaccination: a systematic review. *Pituitary* **27**, 970–985 (2024).
91. Menotti, S., di Filippo, L., Terenzi, U., Chiloiro, S. & De Marinis, L. Hypophysitis in COVID-19: a systematic review. *Pituitary* **27**, 874–888 (2024).
92. Seror, R. et al. EULAR Sjögren's syndrome patient reported index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. *Ann. Rheum. Dis.* **70**, 968–972 (2011).
93. Yum, J., Lee, S.-W., Rhee, Y. & Heo, K. Hypophysitis and central nervous system involvement in association with Sjögren's syndrome along with hypoparathyroidism: a case report. *BMC Neurol.* **24**, 339 (2024).
94. Terrier, B. et al. French recommendations for the management of systemic necrotizing vasculitides (polyarteritis nodosa and ANCA-associated vasculitides). *Orphanet J. Rare Dis.* **15** (Suppl 2), 351 (2020).
95. Li, C., Zou, Y., Lu, X., Wang, G. & Shu, X. Pituitary dysfunction in patients with ANCA associated vasculitis: prevalence, presentation, and outcomes. *Ther. Adv. Chronic Dis.* **11**, 2040622320930636 (2020).
96. Mohammed, H. et al. Hypothalamic and pituitary dysfunction is common in tubercular meningitis: a prospective study from a tertiary care center in Northern India. *J. Neurol. Sci.* **395**, 153–158 (2018).
97. Furin, J., Cox, H. & Pai, M. Tuberculosis. *Lancet* **393**, 1642–1656 (2019).
98. Alves, R. & França, M. Subacute hypophysitis with panhypopituitarism as first presentation of HIV and syphilis coinfection. *Case Rep. Infect. Dis.* **2017**, 1489210 (2017).
99. Spinner, C. D. et al. Acute hypophysitis and hypopituitarism in early syphilitic meningitis in a HIV-infected patient: a case report. *BMC Infect. Dis.* **13**, 481 (2013).
100. Di Stasi, V. et al. Immunotherapy-related hypophysitis: a narrative review. *Cancers* **17**, 436 (2025).
101. Iwama, S., Kobayashi, T. & Arima, H. Management, biomarkers and prognosis in people developing endocrinopathies associated with immune checkpoint inhibitors. *Nat. Rev. Endocrinol.* **21**, 289–300 (2025).
102. Albarel, F., Castinetti, F. & Brue, T. Management of endocrine disease: immune check point inhibitors-induced hypophysitis. *Eur. J. Endocrinol.* **181**, R107–R118 (2019).

103. Chamorro-Pareja, N., Faje, A. T. & Miller, K. K. Pituitary complications of checkpoint inhibitor use. *Endocrinology* **165**, bqae084 (2024).
104. Faje, A. et al. Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab-associated hypophysitis. *Eur. J. Endocrinol.* **181**, 211–219 (2019).
105. Iwama, S. et al. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. *Sci. Transl. Med.* **6**, 230ra45 (2014).
106. Faje, A. T. et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. *Cancer* **124**, 3706–3714 (2018).
107. Levy, M. et al. Anti-PD1 and anti-PDL1-induced hypophysitis: a cohort study of 17 patients with longitudinal follow-up. *J. Clin. Med.* **9**, 3280 (2020).
108. Kotwal, A. Hypophysitis from immune checkpoint inhibitors: challenges in diagnosis and management. *Curr. Opin. Endocrinol. Diabetes Obes.* **28**, 424–427 (2021).
109. Faje, A. T. et al. Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. *J. Clin. Endocrinol. Metab.* **99**, 4078–4085 (2014).
110. Albarel, F. et al. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. *Eur. J. Endocrinol.* **172**, 195–204 (2015).
111. Yamamoto, M. et al. Adult combined GH, prolactin, and TSH deficiency associated with circulating PIT-1 antibody in humans. *J. Clin. Invest.* **121**, 113–119 (2011).
112. Kanie, K. et al. Modeling of T cell-mediated autoimmune pituitary disease using human induced pluripotent stem cell-originated organoid. *Nat. Commun.* **16**, 7900 (2025).
113. Bando, H. et al. Involvement of PIT-1-reactive cytotoxic T lymphocytes in anti-PIT-1 antibody syndrome. *J. Clin. Endocrinol. Metab.* **99**, E1744–E1749 (2014).
114. Urai, S., Iguchi, G. & Takahashi, Y. Anti-PIT1 hypophysitis after immune checkpoint inhibitor treatment. *Nat. Rev. Endocrinol.* **21**, 265–266 (2025).
115. Pagnoux, C. et al. Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. *Arthritis Rheumatol.* **67**, 1117–1127 (2015).
116. Walsh, M. et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N. Engl. J. Med.* **382**, 622–631 (2020).
117. Baughman, R. P. et al. Monitoring of nonsteroidal immunosuppressive drugs in patients with lung disease and lung transplant recipients. *Chest* **142**, e1S–e111S (2012).
118. Kyriacou, A., Gnanalingham, K. & Kearney, T. Lymphocytic hypophysitis: modern day management with limited role for surgery. *Pituitary* **20**, 241–250 (2017).
119. Honegger, J. et al. Treatment of primary hypophysitis in Germany. *J. Clin. Endocrinol. Metab.* **100**, 3460–3469 (2015).
120. Khaleghi, M. et al. Successful treatment of medically and surgically refractory lymphocytic hypophysitis with fractionated stereotactic radiotherapy: a single-center experience and systematic literature review. *Pituitary* **27**, 213–229 (2024).
121. Krishnappa, B. et al. Glucocorticoid therapy as first-line treatment in primary hypophysitis: a systematic review and individual patient data meta-analysis. *Endocr. Connect.* **12**, e220311 (2022).
122. Chiloiro, S. et al. Hypophysitis outcome and factors predicting responsiveness to glucocorticoid therapy: a prospective and double-arm study. *J. Clin. Endocrinol. Metab.* **103**, 3877–3889 (2018).
This is the only clinical trial in hypophysitis to compare patients treated with glucocorticoids with untreated patients (12 and eight patients, respectively). Endocrine and radiological outcomes as well as adverse effects of treatment were evaluated.
123. Liu, D. et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin. Immunol.* **9**, 30 (2013).
124. Beuschlein, F. et al. European Society of Endocrinology and Endocrine Society joint clinical guideline: diagnosis and therapy of glucocorticoid-induced adrenal insufficiency. *Eur. J. Endocrinol.* **190**, G25–G51 (2024).
125. Oray, M., Abu Samra, K., Ebrahimiadib, N., Meese, H. & Foster, C. S. Long-term side effects of glucocorticoids. *Expert. Opin. Drug. Saf.* **15**, 457–465 (2016).
126. Yang, G.-Q. et al. Recurrent autoimmune hypophysitis successfully treated with glucocorticoids plus azathioprine: a report of three cases. *Endocr. J.* **58**, 675–683 (2011).
127. Vakharia, J. D. et al. A novel approach to hypophysitis: outcomes using non-glucocorticoid immunosuppressive therapy. *Eur. J. Endocrinol.* **189**, 309–317 (2023).
128. Castinetti, F. et al. Endocrine side-effects of new anticancer therapies: overall monitoring and conclusions. *Ann. Endocrinol.* **79**, 591–595 (2018).
129. Abla, O. Langerhans cell histiocytosis: promises and caveats of targeted therapies in high-risk and CNS disease. *Hematology* **2023**, 386–395 (2023).
130. Cournoyer, E. et al. Dabrafenib and trametinib in Langerhans cell histiocytosis and other histiocytic disorders. *Haematologica* **109**, 1137–1148 (2024).
131. Hazim, A. Z. et al. Efficacy of BRAF-inhibitor therapy in *BRAF*^{V600E}-mutated adult langerhans cell histiocytosis. *Oncologist* **25**, 1001–1004 (2020).
132. Goyal, G. et al. Erdheim–Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. *Blood* **135**, 1929–1945 (2020).
133. Albarel, F. et al. Evaluation of an individualized education program in pituitary diseases: a pilot study. *Eur. J. Endocrinol.* **183**, 551–559 (2020).
134. Nessan, V. J., Jacoway, J. R., Lauttman, R. J., Swintak, E. F. & Buhler, J. E. Biopsy of minor salivary glands in the diagnosis of sarcoidosis. *N. Engl. J. Med.* **301**, 922–924 (1979).

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F.C., L.M., B.T., F.A., R.A., T.G. and P.-A.J. researched data for the article. F.C., L.M., T.C., H.D., M.E., T.B., P.-A.J. and N.S. contributed substantially to discussion of the content. F.C., L.M., B.T., F.A., R.A. and T.G. wrote the article. F.C., T.C., H.D., M.E., T.B., P.-A.J. and N.S. reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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