Hypophysitis (Including IgG4 and Immunotherapy)

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Abstract

Hypophysitis is characterized by inflammation of the pituitary gland that can be primary (PH) or secondary (SH) to other diseases or following drug administration. It may also be classified according to anatomical and histopathological criteria, leading to variable degrees of hypopituitarism and/or compressive symptoms to nearby structures. There has recently been an increase in the number of hypophysitis cases, raising the interest on the spectrum of its pathogenesis, clinical, biochemical/endocrinological, and imaging features. However, the use of conventional biomarkers, including currently utilized pituitary autoantibodies, has relatively limited diagnostic accuracy. Lymphocytic hypophysitis (LH) is the commonest cause of PH, whereas IgG4-related hypophysitis is increasingly being recognized. Histiocytosis and granulomatous diseases are the most frequent causes of SH, although infections and lymphoma have also been reported. The increasing use of immune checkpoint inhibitors in oncology is associated with a high incidence of hypophysitis, providing further understanding of its pathogenesis. Hy-

pophysitis can occur silently and be easily missed, potentially leading to substantial morbidity or mortality due to adrenal insufficiency, requiring a high index of clinical suspicion and timely initiation of appropriate treatment. In most cases of LH or drug-induced hypophysitis, active surveillance along with replacement of established hormonal deficiencies is needed. In the presence of compressive and/or evolving symptoms, treatment with glucocorticoids either alone or in combination with other immunosuppressive agents can be used. Surgical decompression is reserved for nonresponsive cases with threatened vital structures. Timely diagnosis and intervention are important to minimize disease-related morbidity and mortality. We aimed to review current concepts and recent developments in the pathogenesis, diagnosis, and management of hypophysitis.

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Introduction

Hypophysitis is a heterogenous condition that develops secondary to chronic or acute inflammation of the pituitary, resulting to varying degrees in hypopituitarism and/or symptoms/signs related to sella compression [1, 2]. Hypophysitis is traditionally classified using anatomi-

Table 1. Classification of hypophysitis, incidence, histopathological characteristics, imaging, and treatment

Causes	Incidence	Histopathology	Imaging	Treatment
PH				
LH [1, 3]	76–86% of all PH; 1/7–9 × 10 ⁶ cases	focal or diffuse infiltration of lymphocytes and occasional plasma cells, eosinophils, and fibroblasts; pituitary fibrosis and atrophy may occur in later stages of the disease	isointense in T1-weighted images; suprasellar extension with alteration of the optic chiasm (64% of cases); thickening of the pituitary stalk	hormone replacement treatment in case of hypopituitarism; high-dose glucocorticoid therapy; surgery for nonresponders
IgG4H [26, 93]	30% of all PH; 0.28–1.08/10 ⁵ cases	mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with >10 IgG4-positive cells/high-power field and storiform fibrosis	the radiological appearance does not help differentiate between different types	high-dose glucocorticoid therapy; hormone replacement treatment in case of hypopituitarism; B cell-depleting therapies
GH [1, 56, 71]	20% of all PH; 1/10 × 10 ⁶ cases	large numbers of multinucleated giant cells and histiocytes with granuloma formation	isointense in T1-weighted images; suprasellar extension (67% of cases); pituitary enlargement is the commonest feature; contrast enhancement and pituitary stalk thickening	glucocorticoid therapy appears to be less effective compared with LH while surgical resection leads to better symptom resolution
XH [1, 3, 71]	3% of PH with only 27 cases reported in the literature	foamy histiocytes (lipid-rich macrophages) without presence of granulomas, plasma cells, or small round mature lymphocytes; pituitary fibrosis may be seen in later stages of the disease	hypointense in T1-weighted images; pituitary stalk displacement without thickening	glucocorticoid therapy appears to be less effective compared to LH, but limited clinical experience; complete, partial or no recovery from mass effect of symptoms, but endocrine deficiencies seldom recover
NH [10]	extremely rare, <1% (4 case reports)	diffuse nonhemorrhagic necrosis with surrounding lymphocytes, plasma cells, and eosinophils	lack of enhancement of the enlarged pituitary gland in T1-weighted images; thickening of the pituitary stalk	hormone replacement treatment in case of hypopituitarism
SH				
<i>Drugs</i>				
ICIs (anti-CTLA-4 and anti-PD-1/PD-L1) [27, 28, 70]	1.5–17% of cases with ipilimumab and 0.5–1.5% with PD-1/PD-L1	T cell infiltration and IgG-dependent complement fixation and phagocytosis; CTLA-4-related hypophysitis; complement fixation, macrophage infiltration, and lymphocyte activation (type II and IV hypersensitivity reaction)	no obvious radiological patterns; diffuse enlargement of the pituitary (up to 60–100% of baseline size); enhancement after gadolinium; suprasellar extension with compression and displacement of chiasm is uncommon; posterior pituitary is preserved in most cases	in milder dysfunction: hormone replacement treatment; in severe or life-threatening cases: high-dose glucocorticoids; discontinuation of the ICI
Others: interferon-alpha, ustekinumab, ribavirin				
<i>Systemic diseases</i>				
Sarcoidosis [89]	0.5% of cases	noncaseating granulomas	normal; thickening of the pituitary stalk; suprasellar lesion	treatment of the underlying disease
Granulomatous polyangiitis [18, 90]	rare and late manifestation of the disease	necrotizing granulomas and vasculitis in small- and medium-sized blood vessels	enlarged pituitary gland; heterogenous contrast enhancement	treatment of the underlying vasculitis (steroids, cyclophosphamide)
LCH [18]	40% of cases; 1–2 × 10 ⁶ new cases	infiltration of the pituitary with Langerhans cells, eosinophils, neutrophils, small lymphocytes, and histiocytes	infundibular enlargement; suprasellar mass; absence of the bright spot of the posterior pituitary	prednisone, alone or in combination with vinblastine, cladribine, and vemurafenib; desmopressin; hormone replacement treatment
ECD (rare multisystem non-Langerhans cell form) [32, 33]	50–70% of cases	histiocytes with non-Langerhans features	enlarged pituitary stalk and dural tail sign; hyperintensities in T2-weighted images with and without post-gadolinium enhancement	vemurafenib, interferon-alpha, dabrafenib, trametinib, cobimetinib, cladribine, cyclophosphamide, and glucocorticoids
Anti-PIT-1 antibody syndrome [34]	no data	pathogenesis similar to LH	pituitary enlargement with symmetrical expansion and intense and homogeneous enhancement of the pituitary mass with gadolinium; presence of dural tail sign; pituitary stalk is thickened but not deviated	self-limiting and spontaneous remissions can occur; glucocorticoids and rarely surgery (when visual troubles); immune-suppressive drug
Rosai-Dorfman disease (a rare histiocytic disorder) [36]	no data	plasma cell infiltration, mixed with lymphocytes, large histiocytes with foamy cytoplasm, and Touton giant cells	isointense T1- and T2-weighted images and intensely enhancing with gadolinium	surgery, radiotherapy, steroids, immunosuppressive drugs, or interferon-alpha and cladribine
Tolosa-Hunt syndrome [37]	1–2/10 ⁶ cases	nonspecific granulomatous or nongranulomatous inflammation	enlargement of the pituitary with massive infiltration or mimicking adenoma involving the cavernous sinus	glucocorticoids
Cogan's syndrome [3]	no data	granulomatous infiltration	enlargement of pituitary gland and thickening of stalk	glucocorticoids
Non-Hodgkin B cell lymphoma [21–23]	33 cases	B cell infiltration	diffusely enlarged pituitary gland with invasion of both cavernous sinuses	disease-specific treatment
Others: Crohn's disease, thymoma, infections (bacterial, viral, fungal)				

ECD, Erdheim-Chester disease; ICI, immune checkpoint inhibitor; IgG4H, IgG4 hypophysitis; LCH, Langerhans cell histiocytosis; LH, lymphocytic hypophysitis; NH, necrotizing hypophysitis; PH, primary hypophysitis; SH, secondary hypophysitis; XH, xanthomatous hypophysitis.

cal (adenohypophysitis, infundibulo-neurohypophysitis, and panhypophysitis), histopathological (lymphocytic, granulomatous, xanthomatous, IgG4, and necrotizing), or etiological (primary hypophysitis [PH] or secondary hypophysitis [SH]) criteria [3] (Table 1). Primary forms are characterized by an inflammatory process confined to the pituitary, whereas secondary forms develop secondary to systemic diseases, immunotherapeutic drugs, or other sella-related pathologies [1, 3].

In recent years, several new causative entities have been described. IgG4-related disease (IgG4-RD) and the introduction of immune checkpoint inhibitors (ICIs) as cancer therapies have prompted an increased interest in the role of inflammatory processes as a cause of SH [4, 5].

Hypophysitis is a heterogenous entity that can be diagnosed with certainty following pituitary biopsy. However, the combination of clinical presentation and biochemical/hormonal abnormalities along with imaging findings is mostly used because biopsy can be associated with considerable morbidity. As the pathogenesis of PH remains incompletely understood, treatment is aimed at amelioration of compressive effects and replacement of existing or evolving hormonal deficits, whereas specific treatment is administered to SH. In this review we summarize the current literature, including recently described causes of hypophysitis, and address areas of uncertainty along with anticipated diagnostic and therapeutic developments.

Methods

We performed a PubMed-based search up to October 2019 using the terms “hypophysitis,” “adenohypophysitis/infundibulo-hypophysitis,” “IgG4,” “granulomatous,” “immune checkpoint,” “CTLA-4,” and “PD-1/PD-L1” combined with “hypophysitis,” “hypopituitarism,” and “diabetes insipidus,” producing 1,102 articles. We used filters to select articles in English ($n = 963$), related to humans ($n = 751$), and published the last 15 years ($n = 426$). Further shortlisting was based on their relevance based on the abstract, and after duplicate removal we identified 303 full-text articles (102 reviews/metanalyses, 188 case reports or case series, and 13 clinical studies, of which 85 were regarded as most relevant based on the full text (Fig. 1).

Results

Variants of Hypophysitis

The classification of hypophysitis is challenging and sometimes not clearly defined. Better understanding of the pathophysiological mechanisms and histopathologi-

Fig. 1. Flow diagram of the PubMed database search.

cal findings has led to new consideration and reclassification for several forms of hypophysitis. Often, the clinical distinction between the different subtypes is difficult without biopsy as radiological and hormonal features can be incongruent with one another and with pathological findings.

PH classification is also still evolving since some consider PH variants to be truly distinct entities or idiopathic forms, whereas others consider them to be a different expression of the same autoimmune process due to the possible occurrence of mixed forms [6]. SH is caused by a variety of inflammatory, infectious, vascular, and neoplastic conditions or as an adverse effect of various med-

ications. Autoimmune hypophysitis results from autoimmunity-mediated destruction of the pituitary gland and is the commonest form of hypophysitis, including most cases of the PH category as well as the systemic autoimmune diseases of the SH forms [7].

Primary Forms

Hypophysitis is relatively rare, accounting for approximately 0.24–0.93% of all pituitary diseases [4, 8] – with its incidence constantly increasing with the widespread use of ICIs – and 0.4% of pituitary surgical cases [9]. PH is the commonest form of autoimmune hypophysitis [7]. PH has an incidence of 1/9 million/year and is classified according to etiology, anatomical location, and histopathology [4, 9]. Lymphocytic hypophysitis (LH) is the commonest subtype, whereas other subtypes of PH include granulomatous hypophysitis (GH), IgG4 hypophysitis (IgG4H), xanthomatous hypophysitis (XH), and necrotizing hypophysitis (NH) based on histological criteria [1, 3, 10] (Table 1). Classification by anatomical location of the pituitary includes adenohypophysitis, infundibulo-neurohypophysitis, and panhypophysitis.

LH is the commonest cause of PH, accounting for 76–86% of cases, whereas XH represents one of the rarest forms of PH, with 27 reported cases [11, 12]. It is unclear whether XH constitutes a distinct entity or a continuum of the autoimmune/lymphocytic spectrum. Lately, XH has been considered an inflammatory condition most likely related to partial rupture of a Rathke’s cleft cyst being classified as SH [13]. GH is a chronic inflammatory condition with an incidence of 1/10 million affecting mainly females [14]. GH is considered either a primary entity, idiopathic GH, or secondary to another pathology and constitutes a diagnosis of exclusion. In a review of 82 cases, GH was associated with pituitary lymphocytic infiltration and a mean age at presentation of 43 years [15].

NH is the rarest form of PH (0.6%), with a female/male ratio of 3:1, of unknown etiology that can occur as SH or ICI-induced hypophysitis [6, 16, 17].

Mixed forms of hypophysitis are observed in 4% of PH cases [6]. Lymphogranulomatous hypophysitis may include features of LH and GH, but most likely presents a transition from an initial lymphocytic infiltrative pattern of LH to a more granulomatous, chronic inflammatory pattern [6]. Xanthogranulomatous hypophysitis contains both foamy xanthoma cells and multinucleated giant cells with cholesterol clefts and hemosiderin deposits [6]. XH is the earlier manifestation, followed by xanthogranulomatous hypophysitis changes that occur later during the course of the disease [13].

Table 2. Diagnostic criteria for IgG4H

Criteria	
Histopathology	mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with >10 IgG4-positive cells/high-power field
MRI	sella mass or thickened pituitary stalk
Biopsy	involvement of other organs
Serology	IgG4 > 140 mg/dL
Treatment	clinical and radiological improvement with corticosteroids
Established diagnosis	1 or 2+3 or 2+4+5
IgG4H, IgG4 hypophysitis; MRI, magnetic resonance imaging.	

Secondary Forms

SH results from drug administration, autoimmune diseases, systemic inflammatory processes, or infections [1, 3, 10] (Table 1). After excluding drug-induced hypophysitis, the commonest cause is granulomatous disease. Most pituitary granulomas are due to a specific entity such as histiocytosis, sarcoidosis, syphilis, tuberculosis, or in the context of granulomatous polyangiitis. Infiltrative diseases such as Langerhans cell histiocytosis (LCH) [18] and rarely hemochromatosis are also implicated [19]. SH may be diagnosed in preexisting sella pathologies [20]. Pituitary infections complicated by SH develop via hematogenous spread, contiguous extension to the central nervous system, or following cranial surgery. HIV- and neurosyphilis-induced hypophysitis has also been reported [16–18]; primary pituitary lymphoma may also present as hypophysitis [21–23].

New Causes of Hypophysitis

Recently, IgG4H either isolated or in the context of IgG4-RD has also been described [21, 22, 24]. Its incidence is 0.28–1.08/100,000 patients, comprising 30% of all hypophysitis and 4% of all hypopituitarism cases [17, 18]; however, it may be underreported, as histological/immunohistochemical analysis revealed that 41.4% of LH cases fulfilled the criteria for IgG4H [25]. It usually occurs in the 7th decade with a male predominance [3]; a distinct subset of IgG4-RD with female predominance has also been described [25]. The diagnosis of IgG4H is confirmed by characteristic histopathological findings at pituitary biopsy, and it is considered a subtype of autoimmune hy-

pophysitis. Since pituitary biopsy is an invasive procedure, specific diagnostic criteria have been proposed including histopathological findings, radiological findings on magnetic resonance imaging (MRI), serum IgG4 levels, and response to glucocorticoids [26] (Table 2).

Hypophysitis is one of the commonest endocrinopathies associated with ICI mainly observed with the anti-CTLA-4 agent ipilimumab [9, 27, 28]. Its incidence varies between 0.5%-18%, and is dose-dependent, ranging from 0.5% with a dose of 3 mg/kg, up to 18% with a dose of 10 mg/kg being more frequent in men and the elderly [2, 9, 27]. In one meta-analysis of 6472 patients treated with ICI, only 1.3% developed hypophysitis [29], whereas in another 5.6% of 19,922 patients treated with ipilimumab developed hypophysitis compared to 0.5–1.5% treated with anti-PD-1/PD-L1 agents [30]. ICI-induced hypophysitis is less common with anti-PD-1/anti-PD-L1 monotherapy with a 4.8% prevalence in patients treated with the anti-PD-1 agent pembrolizumab [29]. The median time of onset of hypophysitis for ipilimumab is 9 weeks and 3.3–4.9 months for anti-PD-1s [2]. Combining anti-CTLA-4 with anti-PD-1 agents causes earlier development of hypophysitis [31]. Other drugs that have also been associated with hypophysitis are shown in Table 1.

Erdheim-Chester disease (ECD) is a rare non-LCH form of histiocytosis of clonal myeloid progenitor cells bearing a BRAF-V600E mutation affecting the pituitary [32]. ECD can also give rise to xanthomatous or xanthogranulomatous lesions in the pituitary and must be suspected in apparent XH cases with multiorgan involvement [2]. In a recent French study, 91% of patients had anterior pituitary deficiency, whereas diabetes insipidus (DI) was reported in 33% of cases [33].

In other autoimmune pituitary diseases, specific anterior pituitary defects have been reported. Recently, a unique autoantibody against pituitary-specific transcription factor 1 (PIT-1) was detected in patients with acquired defects of growth hormone, prolactin, and thyroid-stimulating hormone (TSH) [34, 35]. This syndrome named “anti-PIT-1 antibody syndrome” is considered to be a cytotoxic T cell-mediated autoimmune process causing hypophysitis (anti-PIT-1H) [34, 35]. The following criteria have been suggested for the diagnosis of anti-PIT-1H [34]: (1) acquired specific growth hormone, TSH, and prolactin deficiencies without impairment of other pituitary axes; (2) circulating anti-PIT-1 antibodies or PIT-1-reactive cytotoxic T lymphocytes; (3) underlying diagnosis of a thymoma or another malignant neoplasm exhibiting ectopic expression of anti-PIT-1 antibodies. A definitive diagnosis is established if criteria 1 and 2 are

Fig. 2. Histopathological image of a case with lymphocytic hypophysitis. Lymphoplasmacytic infiltration and disruption of the normal architecture of the anterior lobe of the pituitary gland.

met, whereas the presence of criterion 1 alone suggests a probable diagnosis. Criterion 3 may help the diagnosis and clarify pathogenesis, but may not be necessarily obvious at the time of diagnosis based on endocrine abnormalities. Other rarer causes of SH are presented in Table 1 [36, 37].

Pathogenetic Mechanisms

LH is an immune-mediated inflammatory disorder characterized by diffuse infiltration of the pituitary by lymphocytes and variable degrees of fibrosis [7] (Fig. 2). Several pituitary antibodies against alpha-enolase, gamma-enolase, pituitary gland-specific factors 1 and 2, secretogranin 2, chorionic somatomammotropin, and corticotroph-specific transcription factor (TPIT) have been described [6, 38, 39]. In addition, anti-hypothalamic antibodies targeting corticotrophin-releasing hormone-secreting cells as well as antibodies directed against somatotroph, lactotroph, gonadotroph, and corticotroph cells causing selective hormonal deficiencies have also been identified [6]. However, the pathogenicity of these antibodies is not yet confirmed due to lack of high sensitivity and specificity [6]. Recently, two different patterns of immunological involvement have been identified in LH patients demonstrating higher numbers of T than B lymphocytes [40]. The first is an autoimmune process with T helper cell predominance without regulatory T cells and with few B lymphocytes with CD3+ T lymphocytes also costaining for CD4 in this pattern of LH. In the second, the lymphocytic infiltration is more organized, forming

Fig. 3. A Immune checkpoint inhibitors, the CTLA-4 pathway. **a** The tumor-associated antigen is presented by the major histocompatibility complex (MHC) on the antigen-presenting cell (APC) and recognized by the T cell receptor (TCR) of the T cell. Binding B7 on the APC with the CD28 receptor on the T cell is the second signal required for the activation of the T cell and the initiation of the immune response against the tumor cells. **b** CTLA-4 is a homolog of CD28 and limits proliferative response of activated T cells competing with CD28 for ligand B7. This inhibition occurs in response to binding of B7 on APC with CTLA-4 receptor on the T cell and interrupts the second signal. **c** Anti-CTLA-4 antibodies block CTLA-4 and restore T cell activation and proliferation.

B Immune checkpoint inhibitors, the PD-1 pathway. PD-1 is an immune cell-specific surface receptor, and ligands for PD-1 (PD-L1 and PD-L2) are associated proteins that are found on APCs and cancer cells. When bound to a ligand, PD-1 lowers the threshold for apoptosis, induces anergy via blunted TCR signaling, and generally leads to T cell depletion. **a** In certain tumor cells, upregulation of PD-L1 expression has been observed, which leads to increased inhibition of T cell activity in favor of tumor cell survival. **b** A monoclonal antibody against PD-1 can block this pathway and result in upregulation of immune response and inhibition of tumor growth. Figure reproduced with permission of S. Karger AG, Basel from the original source [44].

germinal centers with a relatively higher number of B lymphocytes, whereas most CD3+ cells stain positive for CD8.

The pathogenesis of XH remains unclear owing to the extremely small case numbers, and although it was first thought to be due to an infectious agent, more recent work suggest that XH may be a reactive hypophysitis occurring secondarily to a ruptured Rathke's cleft cyst [6, 12, 41]. The histological findings of a metaplastic epithelium support this hypothesis. However, the precise etiology for rupture of a Rathke's cleft cyst remains unclear, although an association with pituitary apoplexy has been postulated.

The pathophysiology of ICI-induced hypophysitis is not well understood. Although it is conceivable that activation of the immune system may aggravate autoimmunity, this does not explain why hypophysitis is more frequently observed with the anti-CTLA-4 agent ipilimumab compared to anti-PD-1/PD-L1 agents [2, 4, 42].

Recent studies in mouse and human pituitary glands have revealed that anti-CTLA-4 hypophysitis is characterized by the presence of circulating anti-pituitary antibodies and lymphocytic infiltration of the gland [43]. Ectopic expression of CTLA-4 has also been observed in the normal hypophysis in mice, particularly in prolactin- and TSH-secreting cells [43], as well as in hypophysitis and adenomas of the human pituitary gland [17, 44] (Fig. 3).

Anti-PIT-1H is associated with circulating anti-PIT-1 antibodies, which are specific markers for this condition. However, cytotoxic T lymphocytes are actually responsible for its development as circulating antibodies do not exhibit cytotoxic properties, but rather serve as biomarkers for anti-PIT-1H [45]. Recent experiments have demonstrated that PIT-1 protein epitopes are presented by the MHC/HLA class I on the pituitary cells, further suggesting cytotoxic T lymphocyte-mediated destruction in this disorder [45].

Diagnosis of Hypophysitis

The only definitive way to provide an unequivocal diagnosis of PH is through pituitary biopsy and histopathological examination [1] (Fig. 2). However, the procedure is invasive and may not be necessary unless the management outcome of biopsy outweighs its risks. In daily practice, clinical, biochemical/endocrinological, and imaging features should be enough to formulate a differential diagnosis and guide treatment accordingly. The histopathology of LH demonstrates the characteristic infiltration of lymphocytes into the pituitary gland, in the interstitium and pituitary acini, occasionally arranging themselves into lymphoid follicles with germinal centers [6, 46]. The density of lymphocytes is higher in LH compared to other forms of PH, and the lymphocytes can often be accompanied by plasma cells [38, 46]. The end result of LH is pituitary fibrosis, which can often be severe. The amount of lymphocyte infiltration correlates inversely with the degree of fibrosis. XH is characterized by the presence of lipid-rich foamy histiocytes with a variable number of lymphocytes [1, 47]. The diagnosis of XH is only confirmed on tissue sections demonstrating foamy (xanthomatous) macrophages with or without cholesterol clefts, admixed with variable amounts of multinucleated giant cells [12]. In GH the pituitary is infiltrated by histiocytes, multinucleated giant cells, and lymphocytes along with plasma cells [15, 39, 48]. The histopathology of NH reveals extensive areas of necrosis with infiltration of lymphocytes, plasmacytes, and few eosinophils leading to fibrosis [6, 49].

Clinical and Endocrine Findings

Differential diagnosis of the variants of hypophysitis is not always possible due to significant overlap between the clinical symptoms and absence of pathognomonic characteristics. Sex predominance and age at presentation can be additional criteria as LH, GH, and XH occur more frequently in females (female/male ratio of 8.5:1) [4, 50–52]. Many cases of LH (40%) occur in late pregnancy or in the peripartum period [4, 50, 52], whereas GH occurs in older age and is not associated with pregnancy. Similarly to LH, XH occurs mainly during the 4th decade. Unlike pituitary adenomas, the extent of hormonal impairment in hypophysitis is often disproportionate to the size of the lesion on MRI [4, 53, 54].

Headache (50%) is the most frequent symptom in any type of PH, followed by adrenal insufficiency (10–40%) and hyperprolactinemia (20%) [35, 37]. In LH, adrenocorticotrophic hormone followed by TSH deficiency are most commonly reported [1, 55]. It has been suggested that hyperprolactinemia is predominantly seen in the

acute phase of LH [53]. Symptoms related to posterior pituitary infiltration or the stalk are less frequent [4]. In GH, headaches are found in 61%, visual changes in 40% [3, 15, 56], polyuria/polydipsia in 27%, and cranial nerve palsies in 27% of cases [3]. In XH, visual disturbances and DI are rarely reported and anterior pituitary impairment is less severe compared to LH [38, 47, 57]. In contrast to LH, gonadotropin and growth hormone deficiencies are common in XH [38]. Involvement of the cavernous sinus with ophthalmoplegia is relatively rare [55, 58]. Although the clinical and imaging features are similar to other forms of hypophysitis, NH is more likely to present more acutely with mass effect symptoms (e.g., eye pain, visual defects) or even as aseptic meningitis [10, 38].

In IgG4H, anterior pituitary deficiency and DI develop in 48% [59]. Patient history and clinical presentation are useful tools in differentiating IgG4H from LH [1, 60]. IgG4-RD can cause panhypopituitarism, anterior hypopituitarism, or isolated DI in 50, 25, and 18% of cases, respectively [61, 62]. The diagnosis of ICI-induced hypophysitis is based on recent use of these drugs in patients with malignancies. The commonest symptoms include fatigue and headaches in 59–73% and 21–80% of cases, respectively, whereas visual disturbances and DI are relatively rare [9, 43, 63–65]. Most cases are diagnosed during regular follow-up of pituitary function performed before every cycle of therapy for at least the first 3 months [1]. Patients with ICI-induced hypophysitis usually present with TSH (84%), adrenocorticotrophic hormone (80%), and gonadotropin (76%) deficiency [39, 65].

In SH, clinical presentation may not be disease-specific. In sarcoidosis-induced hypophysitis hypogonadism (87.5–89%), hypothyroidism (56%), hypocortisolism (37%), and growth hormone deficiency (30%) are common. The commonest endocrine abnormality, reported in 30% of patients with LCH, is DI, although anterior pituitary deficiencies can occur either at presentation or during follow-up [18, 66, 67]. These patients usually have multiorgan and craniofacial involvement, although localized disease of the hypothalamic-pituitary region has also been reported [66]. Identification of BRAF-V600E mutation in the peripheral blood or cerebrospinal fluid rules out other pathologies, but cannot distinguish LCH from ECD [68]. The commonest pituitary involvement in hemochromatosis is hypogonadism. Pituitary involvement is a rare and late manifestation of granulomatous polyangiitis, mainly causing hypogonadism and DI [20].

Approximately 30% of infection-induced hypophysitis present with partial or complete hypopituitarism, whereas DI has rarely been reported [20]. After treatment

Fig. 4. **a, b** Magnetic resonance imaging T1 sequence sagittal (**a**) and coronal (**b**) imaging of a patient diagnosed with LH. **c, d** Magnetic resonance imaging T1 sequence sagittal (**c**) and coronal (**d**) imaging 6 months after diagnosis and treatment of replacement with corticoids.

with anti-tuberculous drugs, the pituitary tuberculoma may disappear, with restoration of hypopituitarism in some cases [69].

Clinical manifestations are not always typical of a precise form of hypophysitis and in general severe headaches, visual disturbances due to chiasmal compression, and symptoms of hypopituitarism are the commonest presentations of hypophysitis. Less frequently, inflammation can primarily involve the posterior pituitary and the stalk, presenting with symptoms related to DI. Patients on ICI therapy often present with headache and anterior hypopituitarism, whereas those with IgG4H tend to present with more variable clinical features including headache, visual field defects, fever, weight loss, hypopituitarism, and/or DI. Since several subtypes of hypophysitis may be secondary to a systemic condition or an infiltrate disorder, it is important for the clinician to consider a broad clinical history and physical examination, especially in cancer patients on newer oncological medications.

Imaging Findings

Gadolinium-enhanced pituitary MRI is the preferred modality to define pituitary pathology. MRI is initially performed and monitored during the first 3 months of follow-up and thereafter according to disease progression [70]. Features suggestive of hypophysitis include an intense and enlarged triangular- or dumbbell-shaped homogeneously enhancing gland with a thickened but not deviated stalk and absence of the posterior pituitary bright spot in patients with DI [71]. Empty sella may also represent a late finding in hypophysitis [53, 72]. The presence of pituitary stalk thickening, in the appropriate clinical setting, is perhaps the strongest predictor of an inflammatory process [71]. These features are most prominent in LH that exhibits symmetric pituitary enlargement, pre-contrast homogeneity, and strips of involved area which resembles contrast-enhancing tissue along the dura mater, termed “dural tail” or “meningeal tail” [1, 4, 73] (Fig. 4). MRI-specific findings for GH, albeit less well

described, include pituitary enlargement and pituitary stalk thickening [56]. XH presents as cystic sellar mass, peripherally enhancing on post-gadolinium contrast images [71]. NH shows nonspecific MRI findings, including symmetrical enlargement of the pituitary gland without signs of hemorrhage, and thickened and pathologically enhancing stalk [53].

The imaging appearances on MRI of the different types of PH are quite similar, whereas differentiating hypophysitis from other sellar lesions, mainly pituitary adenoma, is difficult (Table 1) [56]. A radiological score based on eight predictors has been developed to differentiate PH from pituitary adenomas, with a 92% sensitivity, a 99% specificity, and 97% both positive and negative predictive values [53, 55, 74]. The score ranges from -13 to +8, and a score ≥1 is suggestive of an adenoma, whereas a score ≤0 is suggestive of hypophysitis [74] (Table 3). Recently, fluorodeoxyglucose F 18 positron emission tomography is used in patients with inflammatory pituitary conditions, particularly in IgG4-RD and in LCH [15, 61, 94].

Hypophysitis is a challenging radiological diagnosis which should be primarily differentiated from pituitary adenomas, pituitary metastases, and from other sellar/parasellar tumors. MRI is considered the imaging of choice. Presence of pituitary stalk thickening as well as pituitary expansion with gadolinium enhancement are the strongest predictors of an inflammatory process in the pituitary gland. However, in cases of spontaneously resolution, absence of MRI findings at the time of investigation does not rule out long-standing autoimmune hypophysitis, and thus some cases of isolated hypopituitarism may represent a late or “missed” presentation of hypophysitis.

Treatment

The natural history of PH is variable, without therapeutic protocols based on established evidence [55]. Most of the literature refers to LH, whereas data for other histological subtypes are scarce. It is important to distinguish between the acute phase of hypophysitis, which may require systemic treatment, and the chronic phase, which often evolves to fibrosis and pituitary atrophy, for which only treatment of hypopituitarism is needed [53]. Although regular surveillance is recommended for the chronic forms, only 4% of patients with LH had spontaneous remission with recovery of pituitary function, while most required long-term replacement of established hormonal deficiencies [4, 55].

In cases of progressive/recurrent LH, immunosuppressive agents have been used [75], but data on glucocor-

Table 3. Radiological features to distinguish autoimmune hypophysitis from nonsecreting pituitary adenoma (by Gutenberg et al. [74])

Features	Score
Related to pregnancy	
Yes	-4
Pituitary mass volume	
6 cm ³	2
Asymmetry	3
Gadolinium enhancement type	
Medium/high	-1
Gadolinium enhancement features	
Heterogenous	1
Loss of the posterior pituitary bright spot	-2
Enlarged stalk size	-5
Mucosal swelling	2

ticoid administration are controversial [38]. An overall relapse rate following glucocorticoid withdrawal of 38% in PH has been described that developed 2–17 months after tapering, without correlation with glucocorticoid dose or treatment duration [58]. Presence of central DI was considered an unfavorable prognostic factor for response to glucocorticoids [76]. However, a recent study showed that presence of anti-pituitary antibody, central DI, absence of “bright spot” on MRI, and pituitary stalk >3.9 mm correlated with a better responsiveness to glucocorticoids in LH [77].

As long-term treatment with glucocorticoids is associated with adverse effects, glucocorticoid-sparing agents have been used [58]. Azathioprine is most commonly used, leading to pituitary mass reduction in 84% of cases, improvement of anterior/posterior pituitary function in 45 and 41%, respectively, and a 14% overall risk of relapse [78]. Rituximab, an anti-CD20 antibody that specifically depletes B lymphocytes, can be an effective treatment for patients with steroid-refractory B cell-predominant LH [79]. Remission of LH was observed in all reported cases using rituximab, and in one case remission was maintained even 3 years after treatment [79–81]. Glucocorticoid therapy is less effective in GH and XH compared to LH [3, 30].

Surgery should be considered only in cases with serious and progressive visual field deficits and deterioration of visual acuity not responsive to medical treatment [3, 82, 83]. Moreover, surgery provides a histological diagnosis to guide future management [83]. The rate of recurrence/relapse of PH after surgery is 11–25% [3, 41, 51, 52]. Only a few cases of LH have been treated with stereotactic

Table 4. CTCAE in ICI-induced hypophysitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pituitary disorders	asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated	moderate, minimal, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living	severe or medically significant but not immediately life-threatening hospitalization prolongation of existing hospitalization indicated; disabling; limiting self-care	life-threatening consequences; urgent intervention indicated	death

CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitor.

Fig. 5. Therapeutic approach in patients with hypophysitis. ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging.

radiotherapy, leading to resolution of symptoms after 2 weeks to 6 months [39, 66]. Radiation-induced hypopituitarism is observed in 20–30% of patients, typically occurring within the first 5 years following radiosurgery [84].

IgG4-RD should be promptly treated to revert symptoms and prevent fibrosis; prednisone 30–40 mg/day induces remission of symptoms within a few weeks and is then tapered gradually over 2–6 months [85]. However, some patients may benefit from long-term maintenance glucocorticoid therapy, especially in cases of multiorgan

involvement. Rituximab has been used in patients with poor response to glucocorticoids, albeit with higher relapse rates [85]. In some cases of IgG4H, spontaneous remissions have also been described [86].

In ICI-induced hypophysitis, the therapeutic management depends on the grading of the hypophysitis. In mild or moderate cases (grades 1 and 2 according to Common Terminology Criteria for Adverse Events [CTCAE] v4.03), simple surveillance with replacement of pituitary hormonal deficiencies is adequate without interruption

of the ICI. In severe forms (grades 3 and 4 according to CTCAE v4.03), high-dose of glucocorticoids may be required with interruption, at least temporarily, of the ICI agent (Table 4).

Hypophysitis secondary to LCH should be treated with prednisone, alone or in combination with vinblastine, and cladribine, alongside with other pituitary hormone replacements in case of hypopituitarism [20]. Vinblastine and steroid-based therapy are suggested as the first-line options by the Histiocyte Society guidelines (Table 1) [87]. A positive response to the BRAF inhibitor vemurafenib has been described in patients with BRAF-V600E-mutated LCH [88]. The treatment options for ECD include vemurafenib, interferon-alpha, cladribine, and glucocorticoids (Table 1) [2].

Most patients with sarcoidosis are treated with high-dose glucocorticoids, whereas 50% also receive other immunomodulators. In one study only 13% showed improvement of existing pituitary deficiencies, with an all-cause mortality of 8.7% [89]. There is no consensus on the best therapy strategy for granulomatous polyangiitis hypophysitis [3]. Although glucocorticoids with cyclophosphamide are the mostly used, no differences in the outcome of pituitary function are seen when compared with other immunosuppressive agents [90].

An algorithm of the therapeutic approach to hypophysitis is summarized in Figure 5. Treatment with high-dose glucocorticoids may be of value in reducing the mass effect, but there is little evidence of its role in facilitating recovery of pituitary function. Surgery is rarely indicated, but may be considered when glucocorticoid therapy has failed to reduce symptoms of mass effect or when the diagnosis remains questionable and tissue diagnosis is required. Discontinuation of ICI is reserved only for severe cases of hypophysitis as it did not improve the outcome of hypophysitis or hypophysitis-related hypopituitarism when compared to patients who remained on therapy. Patients with IgG4-RD and multiorgan involvement may benefit from long-term physiological glucocorticoid therapy. In cases of progressive or recurrent disease, high-dose glucocorticoid therapy and glucocorticoid-sparing regimens may be considered.

Recent Advances and Evolving Markers

New serological markers are likely to serve as noninvasive diagnostic tools. The HLA markers DQ8 and DR53 are used to identify patients with LH since there is a 23.1-fold increase in DQ8 levels in LH compared to other pituitary pathologies [91]. The role of anti-pituitary antibodies in autoimmune hypophysitis is still debated be-

cause of several methodological problems leading to a low sensitivity and specificity of the method. Recently, a new target autoantigen, anti-rabphilin 3A, was identified in 76% of patients with DI and suspected infundibular LH, but is not widely available yet [92]. Serum anti-pituitary antibodies could however be useful in special cases, helping to avoid an underestimation of autoimmune hypophysitis; these cases include idiopathic hypopituitarism associated with other autoimmune diseases and hyperprolactinemia without pituitary adenoma on MRI or in empty sella syndrome [53].

Conclusion

Hypophysitis is a heterogenous condition with diverse etiologies, although most subtypes develop in the context of a strong autoimmune background. The recognition of new causes, such as IgG4-, anti-PIT-1-, and ICI-induced hypophysitis, as well as the improvement of imaging techniques have led to an increase in its incidence. Replacement of pituitary hormonal deficiencies is the sole medical treatment in most mild and/or chronic cases, but in severe acute presentations, presence of mass effects, and/or progressive/recurrent cases, treatment with glucocorticoids and/or other immunosuppressive agents is required. In cases of SH, disease-specific treatment may also be needed. Although current biomarkers are not disease-specific, it is expected that serological markers such as HLA-DQ8/HLA-DR53 and newer anti-pituitary antibodies will emerge as promising noninvasive diagnostic tools facilitating diagnosis and predicting prognosis and response to glucocorticoids and other evolving treatments.

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