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New causes of hypophysitis

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Hypophysitis is a rare entity characterized by inflammation of the pituitary gland and its stalk that can cause hypopituitarism and/or mass effect. Etiology can be categorized as primary or secondary to systemic disease, but may also be classified according to anatomical and hispathological criteria. Newly recognized causes of hypophysits have been described, mainly secondary to immunomodulatory medications and IgG4-related disease. Diagnosis is based on clinical, laboratory and imaging data, whereas pituitary biopsy, though rarely indicated, may provide a definitive histological diagnosis. For the clinician, obtaining a broad clinical and drug history, and performing a thorough physical examination is essential. Management of hypophysitis includes hormone replacement therapy if hypopituitarism is present and control of the consequences of the inflammatory pituitary mass (e.g. compression of the optic chiasm) using high-dose glucocorticoids, whereas pituitary surgery is reserved for those unresponsive to medical therapy and/or have progressive disease. However, there remains an unmet need for controlled studies to inform clinical practice.

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Introduction

Hypophysitis refers to an acute or chronic inflammation of the pituitary gland and/or its stalk causing pituitary enlargement and varying degrees of hypopituitarism, including diabetes insipidus (DI). This condition is heterogeneous and its pathogenesis remains incompletely understood. In recent years, several new histopathologic and causative agents have been described. Although this condition remains rare, the number of publications has gradually increased and expanded to involve a more gender and age diverse population, largely because of the increased utilization of novel immune checkpoint inhibitors (CPI) for cancer therapies, and the recent recognition of IgG4-related disease (IgG4-RD). However, good quality data remains scarce, and diagnosis and treatment regimens have been diverse due to lack of evidence-based consensus guidelines.

Classification of hypophysitis

The classification of hypophysitis has been challenging because of the overlap in using the term for inflammatory, infiltrative, and neoplastic conditions. Furthermore, imaging features, particularly those of IgG4-RD, can be non-specific and may mimic pituitary adenomas [1,2], Rathke's cleft cyst (RCC) [3,4], empty sella that may be a consequence of previous end-stage hypophysitis [5], and infiltrative conditions, such as sarcoidosis [6]. Hypophysitis can be classified into three categories: etiology, anatomical location, and histopathology (Table 1). Based on etiology, hypophysitis may be caused by primary/idiopathic inflammation confined to the pituitary gland, whereas secondary hypophysitis is a consequence of drugs, autoimmune conditions, systemic inflammatory processes such as sarcoidosis, infections such as tuberculosis, and pituitary adenomas. Hypophysitis classified by anatomic location of the pituitary involvement includes adenohypophysitis, infundibuloneurohypophysitis and panhypophysitis. Classification based on histopathological appearance comprises of several histological subtypes. Lymphocytic hypophysitis is the commonest subtype, followed by xanthomatous hypophysitis, granulomatous hypophysitis, IgG4-related hypophysitis and necrotizing hypophysitis. In this review, we aim to focus on describing secondary hypophysitis induced by drugs and IgG4-related hypophysitis, and discuss optimal diagnostic approaches and therapeutic strategies.

Clinical presentation of hypophysitis

Patients with hypophysitis can present with hypopituitarism and/or mass effect (e.g., headache, with or without nausea, and visual disturbances that include visual field deficits and ophthalmoplegia) [7]. The onset of headache and visual symptoms can be insidious, subacute, or acute, and may mimic pituitary apoplexy [4]. Endocrinopathies are common, and can be life-threatening if not promptly recognized and treated appropriately. The severity of hormonal deficits varies and may be disproportionate to the imaging findings. In contrast to pituitary adenomas [8], there is no predictable order in which anterior pituitary hormone deficits develops, with isolated ACTH deficiency and DI in particular, being recognized presentations [7,9,10]. Patients on CPI therapy, especially ipilimumab, often present with headache and anterior hypopituitarism, whereas those with IgG4-related hypophysitis tend to present with more variable features that include headache, vomiting, nausea, visual field defects, fever, weight loss, hypopituitarism, and/or DI [11–23].

Because several subtypes of hypophysitis may be secondary to a systemic condition or an infiltrate disorder, it is important that the clinician consider a broad clinical history, physical examination, and perform appropriate laboratory evaluation and in some cases, whole-body imaging e.g., CT, MRI and FDG-PET/CT imaging. Taking a careful drug history is essential especially in cancer patients on newer oncological medications, whereas patients with IgG4-RD might manifest with a clinically visible mass due to sialadenitis or orbital disease [24], or painless jaundice due to the compressive effects of autoimmune pancreatitis causing bile duct obstruction [25].

Table 1
Classification of hypophysitis [94].

Etiology	Anatomical location	Histopathology forms
Primary hypophysitis Isolated Associated with autoimmune diseases Polyglandular autoimmune syndrome Systemic lupus erythematosus Sjogren's syndrome Rheumatoid arthritis Primary biliary cirrhosis Atrophic gastritis Autoimmune thyroiditis Autoimmune adrenalitis Type 1 diabetes mellitus Lymphocytic parathyroiditis Idiopathic inflammatory myopathy Temporal arteritis Behcet's disease	*Adenohypophysitis* Inflammation of the anterior pituitary gland; accounts for 65% cases of primary hypophysitis *Infundibulo-neurohypophysitis* Inflammation of the posterior pituitary gland and the stalk; accounts for ~10% cases of primary hypophysitis *Panhypophysitis* Inflammation of the entire pituitary gland; accounts for ~25% cases of primary hypophysitis	Lymphocytic hypophysitis (68%) Granulomatous hypophysitis (20%) Xanthomatous hypophysitis (3%) [a]IgG4-related hypophysitis (4%) Necrotizing hypophysitis (<1%) Mixed forms (lymphogranulomatous, xanthogranulomatous)
Secondary hypophysitis Drug-induced [a]Immune checkpoint inhibitors (CTLA4 Ab, PD-1 Ab) Interferon-α Ribavirin		
Sellar and parasellar lesions Germinoma Rathke's cleft cyst Craniopharyngioma Pituitary adenoma Primary pituitary lymphoma		
Systemic diseases [a]IgG4-related disease Sarcoidosis Granulomatosis with polyangiitis Langerhan's cell histiocytosis [a]Erdheim Chester's disease Inflammatory pseudotumor Takayasu' arteritis Crohn's disease [a]Thymoma (Anti-Pit-1 Antibody syndrome)		
Infections Bacteria Viruses Coxsackie Mycoses Parasites		

[a] New causes of hypophysitis.

Treatment of hypophysitis

The acute phase of hypophysitis, particularly with mass effect (e.g., compression of the optic chiasm and other cranial nerve palsies) and progressive headache are strong indications for emergent treatment. Following confirmation of the mass effect with an MRI scan, treatment with pharmacological

doses of glucocorticoids may be of value in reducing the mass effect, but there appears to be little evidence of its role in aiding the recovery of pituitary function, and may in fact, reduce survival rates in patients with melanoma [26]. By contrast, patients with IgG4-related hypophysitis and multi-organ involvement may benefit from long-term maintenance glucocorticoid therapy. In cases of progressive or recurrent disease, high-dose glucocorticoid therapy and glucocorticoid-sparing regimens, such as alternative immunosuppressive agents such as rituximab [27] or azathioprine [11], or stereotactic radiosurgery [28,29], have been utilized. During the acute phase of hypophysitis, assessment of pituitary hormone secretion should be performed, and appropriate management is imperative for any detected endocrinopathies, particularly acute adrenal insufficiency which could be life-saving. Surgery is generally rarely indicated, but may be considered when glucocorticoid therapy has failed to relieve the mass effect, and when the diagnosis remains questionable and tissue diagnosis is required. The rate of recurrence of the lesion after surgery can be as high as 11–25% [7,30], and post-operative hypopituitarism is more frequent after gross total resection compared to biopsy or partial resection. In cases without compressive symptoms, treatment of hypopituitarism, if present, with hormone replacement therapy, and close monitoring are needed as spontaneous resolution of pituitary enlargement over time has been reported in some cases [7,31,32]. In Fig. 1, we propose a decision tree for managing patients suspected of hypophysitis.

New causes of hypophysitis

Hypophysitis due to drugs

Checkpoint inhibitor therapy are novel monoclonal antibodies targeting immune checkpoints cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein-1 (PD1) and its ligands (PD-L1), and are increasingly used for solid and haematological cancers [33]. These drugs inhibit several regulators of immune activation termed immune checkpoints, thus enhancing the host immune response to tumor cells. However, immune checkpoints also play an important role in maintaining immunological self-tolerance and preventing autoimmune disorders. Because of their mode of action, autoimmune-related adverse reactions can affect numerous organs (e.g. endocrine organs, skin, colon, lungs, and liver) [34]. Hypophysitis is one of the more common of the endocrinopathies associated with CPI therapy [35–37]. Given the increasing use of CPI therapy in oncology and potentially life-threatening endocrinopathies, it is crucial not only for oncologists and endocrinologists, but also for primary care physicians and emergency room providers to be aware of these clinical manifestations. Patients on this therapy with hypophysitis may have other complications of cancer and its treatment that are non-endocrine, hence the pituitary function of these patients should be evaluated if these patients become unwell.

Checkpoint inhibitor-mediated hypophysitis is more frequently reported in men and the elderly [38], and has been more commonly observed with the anti-CTLA-4 agent ipilimumab [38,39]. Its incidence varies between 0.5% and 18%, and is dose-dependent, ranging from 0.5% with a dose of 3 mg/kg to 18% when 10 mg/kg is administered (Table 2). When ipilimumab (3 mg/kg for 4 doses) is combined with the anti-PD-1 agent nivolumab (1 mg/kg for 4 doses followed by 3 mg/kg), the incidence of hypophysitis is ~8% [40]. By contrast, hypophysitis is less common in patients treated with anti-PD-1 or anti- PD-L1 monotherapy [35].

The pathophysiology of immune-checkpoint mediated hypophysitis is not well-understood. Although it is conceivable that general activation of the immune system may cause autoimmune reactions, this does not explain why hypophysitis, which is still relatively rare in spite of its increasing recognition [10], is more frequently observed with ipilimumab compared to other autoimmune endocrinopathies, such as thyroiditis, with anti-PD-1/PD-L1 agents [35–37]. Recent mice data have revealed that immune-checkpoint mediated hypophysitis is characterized by the presence of circulating anti-pituitary antibodies and a lymphocytic infiltration of the gland with anti-CTLA-4 treatment. Ectopic expression of CTLA- 4 (at both RNA and protein levels) has been observed in hypophysis in mice, particularly by prolactin- and TSH-secreting cells [41], and at variable levels in normal human

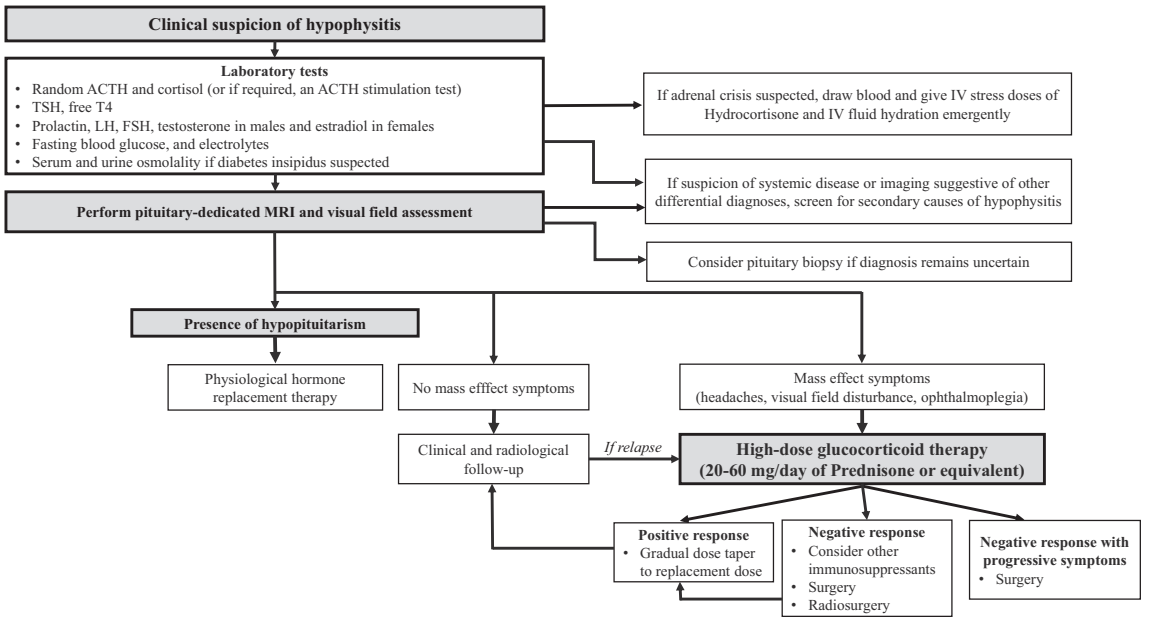

Fig. 1. Clinical evaluation for possible hypophysitis.

Table 2
Summary of incidence of immune-related hypophysitis in recent clinical studies using a variety of immune checkpoint inhibitors.

Studies	Disease treated	Dose	Incidence of hypophysitis
Ipilimumab (anti CTLA-4)			
Hodi et al., 2010 [95]	Melanoma	3 mg/kg Q3w	0.5–1.5%
Bronstein et al., 2011 [96]	Melanoma	3 or 6 or 10 mg/kg Q3w to Q4w	1.7%
Ryder et al., 2014 [97]	Melanoma	0.3, 3 or 10 mg/kg Q4w	8%
Eggermont et al., 2015 [98]	Melanoma	10 mg/kg Q3w	18%
Larkin et al., 2015 [40]	Melanoma	3 mg/kg Q3w	3.9%
Khoja et al., 2016 [99]	Melanoma	0.3–10 mg/kg Q3w to Q4w	1.2%
Ascierto et al., 2017 [100]	Melanoma	10 mg/kg Q3w	2–3%
Brilli et al., 2017 [101]	Melanoma and prostate cancer	3 or 10 mg/kg Q3w	3.3%
Weber et al., 2017 [102]	Melanoma	3 or 10 mg/kg Q3w	10.6%
Barroso-Sousa et al., 2018 [35]	Melanoma, pancreas, RCC, and other solid tumors	Not reported	4.6%
el Majzoub et al., 2018 [103]	Melanoma, lung, GU, GI, hematological, head and neck cancers	Not reported	4.3%
Scott et al., 2018 [104]	Melanoma	3 mg/kg Q3w	6%
Nivolumab (anti PD-1)			
Larkin et al., 2015 [40]	Melanoma	3 mg/kg Q2w	0.6%
Robert et al., 2015 [105]	Melanoma	3 mg/kg Q2w	0.5%
Weber et al., 2017 [102]	Melanoma	3 mg/kg Q2w	1.5%
Barroso-Sousa et al., 2018 [35]	Melanoma, ovarian, RCC, and other solid tumors	Not reported	0.5%
el Majzoub et al., 2018 [103]	Melanoma, lung, GU, GI, hematological, and head and neck cancers	Not reported	0.6%
Pembrolizumab (anti PD-1)			
Reck et al., 2016 [106]	NSCLC	Not reported	0.6%
Robert et al., 2015 [107]	Melanoma	10 mg/kg Q2w or Q3w	0–0.4%
Barroso-Sousa et al., 2018 [35]	Melanoma, gastric, NSCLC, breast, and other solid tumors	Not reported	0.6%
el Majzoub et al., 2018 [103]	Melanoma, lung, GI, GU, hematological, head and neck cancers	Not reported	0%
Ipilimumab + Nivolumab			
Larkin et al., 2015 [40]	Melanoma	3 mg/kg + 1 mg/kg Q3w (4 cycles) then switch to 3 mg/kg Nivolumab or Placebo	7.7%
Sznol et al., 2017 [108]	Melanoma	3 mg/kg Q3w (4 cycles) + 1 mg/kg then 3 mg/kg Nivolumab Q2w until disease progression or unacceptable toxicity	8.5%

GI: gastrointestinal; GU: genito-urinary; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma.

hypophysis, hypophysitis, or adenomatous pituitary cells [42]. The appearance of circulating anti-pituitary antibodies was also observed in patients who developed hypophysitis [41]. This suggests that the administration of anti-CTLA-4 antibodies to patients with high pituitary expression of CTLA-4 can induce hypophysitis via T-cell dependent (type IV) and antibody-dependent (type II) anti-CTLA- 4 immune mechanisms, as well as the humoral immune response [42]. This immune inflammation causes hypophysitis and other endocrinopathies of downstream target organs [43]. For ipilimumab, the median time to onset of immune-checkpoint mediated hypophysitis is 9 weeks after treatment initiation (range 7–20 weeks) [44], while it is ~3.3–4.9 months after initiation of an anti-PD-1 agent [45]. Combining anti-CTLA-4 with anti-PD-1 therapy may cause earlier development of immune-checkpoint mediated hypophysitis [40].

Immune-checkpoint mediated hypophysitis and primary hypophysitis are associated with initial ACTH, LH/FSH and TSH deficits; however, DI is rare in immune-checkpoint mediated hypophysitis

[46,47]. There is a tendency of pituitary enlargement on MRI and visual disturbance in primary hypophysitis, whereas the pituitary gland may be normal in size in immune-checkpoint mediated hypophysitis [38,39,42]. Patients with immune-checkpoint mediated hypophysitis can be asymptomatic or present with non-specific symptoms, such as headache, fatigue, myalgia, confusion, hallucinations, memory loss, anorexia, or symptoms of hypopituitarism [36]. However, visual disturbances and DI are rare [36]. It is imperative that in any patient presenting being unwell on CPI therapy, prompt endocrine assessment (urgent measurements of ACTH and cortisol levels or an ACTH stimulation test, TSH, free thyroxine, electrolytes, fasting plasma glucose, prolactin, LH, FSH, testosterone in males, estradiol in premenopausal females with oligo- or amenorrhea, plasma and urine osmolality if DI is suspected, anti-pituitary antibodies, if locally available), and an MRI scan be performed (Fig. 2). Further details on the acute management of unwell patients on CPI therapy are described in the recent publication of guidelines by the Society for Endocrinology [51].

It is important to stress that low serum cortisol levels can infrequently be found in some cancer patients after recent discontinuation of dexamethasone used as part of their anti-emetic and chemotherapeutic regimens. Hence, if there is a clinical suspicion of adrenal insufficiency, physiological rather than pharmacological doses of glucocorticoid replacement should be initiated [48]. However, if there is a clinical suspicion of acute adrenal crisis without mass effect, emergent stress dosing with IV or IM hydrocortisone (50 mg every 6 to 12 hourly) could be considered together with IV fluid hydration [48], while high-dose prednisone (prednisone 20–60 mg/day or equivalent) should only be considered in patients with mass effect [34,49–51] (Fig. 1). Faje et al. [26] recently reported that high-dose glucocorticoid therapy (>7.5 mg/day of oral prednisone or equivalent during the initial 2 months of therapy) does not confer any advantage to patients with ipilimumab-induced hypophysitis in terms of recovery of pituitary function, but in fact, may be associated with a worse survival. Central hypothyroidism and hypogonadotropic hypogonadism may be transient and recover spontaneously, whereas central adrenal insufficiency tends to be permanent. Measurement of serum IGF-I levels is unnecessary as even if GH deficiency is present, recombinant GH replacement therapy is contraindicated due to the oncological context.

The appearance of immune-checkpoint mediated hypophysitis on MRI, even if not specific, is characterized by the disappearance of the precontrast T1 hyperintensity in the posterior aspect of the pituitary gland, associated with a diffuse enlargement of the whole gland, and variable enlargement of the stalk. The gland typically appears homogeneously hyperintense on T1-weighted postcontrast sequences, and the glandular enlargement may spontaneously resolve several weeks after drug initiation

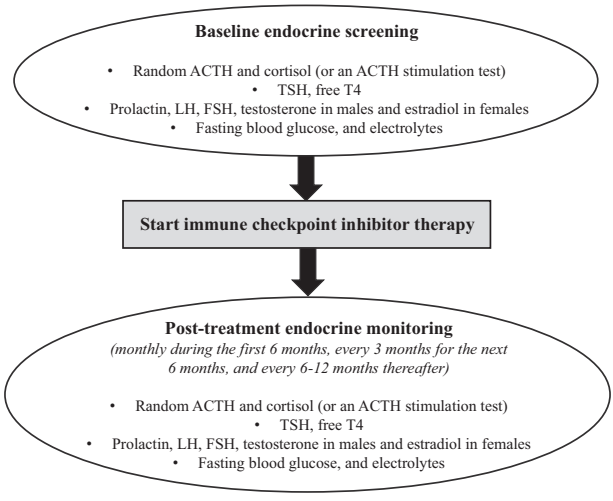

Fig. 2. Endocrine evaluation in patients treated with immune checkpoint inhibitors.

[38] (Fig. 3). Differential diagnoses on MRI include pituitary metastases, pituitary adenoma, pituitary apoplexy, meningioma, leptomeningeal metastases, and granulomatous hypophysitis. In the absence of an abnormal MRI, endocrine evaluation is recommended, and if hypopituitarism is detected, appropriate hormone replacement therapy should be initiated [34,49–51]. In this clinical scenario, the CPI may be continued together with long-term hormone replacement therapy to minimize the impact on progression-free survival of the underlying malignancy [34,49–51].

Current recommendation guidelines [34,49,50] propose long-term follow-up with close monitoring at each appointment for 6 months, then at three-monthly intervals for 6 months and bi-annually thereafter with a repeat MRI at 3 months in order to detect relapses, complications, resolution of disease, and to eliminate the differential diagnosis of pituitary metastasis (Fig. 2). Min et al. [39] demonstrated that discontinuation of ipilimumab did not necessarily improve the outcome of hypophysitis or hypophysitis-related hypopituitarism when compared to patients who remained on therapy, and that recovery of pituitary function was seen in a subset of patients that did not discontinue ipilimumab. If there is evidence of hypopituitarism and an abnormal pituitary gland on MRI causing mass effect, the next cycle of CPI therapy may be delayed as hypophysitis *per se* is not a reason to discontinue therapy. If CPI therapy was withheld, therapy can be resumed in patients with complete or partial resolution of adverse reactions and receiving 7.5 mg of prednisone or less. For those with symptomatic reactions beyond 6 weeks and are unable to reduce glucocorticoid dosing to 7.5 mg of prednisone or its equivalent daily, then permanent discontinuation of therapy can be considered [39].

Hypophysitis due to systemic disease

IgG4-related hypophysitis

IgG4-related hypophysitis is a recently described hypophysitis subtype that forms part of an emerging group of multi-organ IgG4-related fibrosclerotic systemic diseases [52,53]. This disease is characterized by dense infiltration of IgG4-positive plasma cells into the pituitary gland, thickening of the pituitary stalk, diffuse infiltration of the pituitary with lymphocytes, and fibrosis with a “storiform” pattern [4,19,54] (Fig. 4). Pathogenesis of this disease is not well-understood and may involve autoimmunity and/or an abnormal tolerance to unspecified allergens and infectious agents [55]. Pituitary involvement in IgG4-RD was initially believed to be rare [56], with the majority of cases of IgG4-related

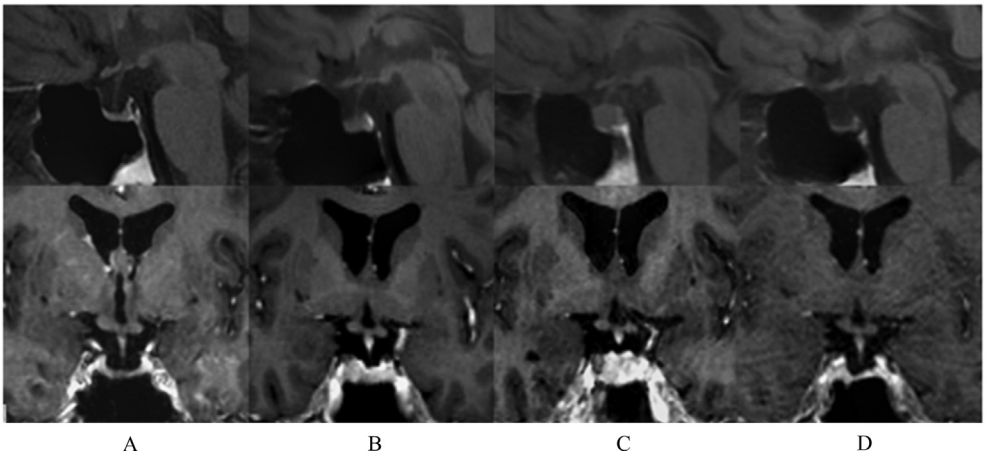

Fig. 3. MRI showing pituitary enlargement followed by spontaneous resolution with ipilimumab therapy. Panel A depicts the pituitary gland 1 month prior to the initiation of ipilimumab. Panel B depicts mild interval pituitary enlargement after 2 cycles of ipilimumab. Panel C depicts further enlargement ~1 week after receiving a third cycle of ipilimumab. Panel D depicts spontaneous resolution of pituitary enlargement ~1 month after receiving a third cycle of ipilimumab. Adapted from Faje AT et al. [38].

hypophysitis being in middle-aged or older males [57]. However, Bando et al. [58] reported a high prevalence of IgG4-related hypophysitis in 170 Japanese patients with hypopituitarism/DI and a clinical diagnosis of hypophysitis (4% and 30% respectively), whereas Bernreuther et al. [59] demonstrated that its prevalence could be as high as 41% in 29 histologically confirmed hypophysitis cases, suggesting that this disease may have been previously underestimated. In 2011, Leporati et al. [17] devised new diagnostic criteria without the need for biopsy by taking into consideration of MRI findings, serologic results, and response to glucocorticoid therapy (Table 3). Since the Leporati criteria was published [17], the number of case reports of IgG4-related hypophysitis has increased in recent years with more than half of the reported cases originating from Japan, raising the possibility of ethnic differences, variability in disease prevalence, and/or increased awareness in certain countries [57].

In the normal pituitary, IgG4 immunopositive plasma cells are not seen. By contrast, in IgG4-related hypophysitis, in addition to the presence of IgG4-positive cells, polymorphs and eosinophils, areas of fibrosis is also an important morphological characteristic [55]. Therefore, it is important to be cautious when diagnosing IgG4-related hypophysitis with only the presence of small numbers of IgG4-positive cells in the lesion because these cells can also be detected in other conditions (e.g., inflammatory, infectious, autoimmune, and neoplastic diseases). Given the scarcity of reports documenting pituitary involvement in IgG4-RD, which defining criteria (clinically and pathologically) that apply will need further investigation. Additionally, elevated serum IgG4 levels is not a specific diagnostic criterion as these levels can also be elevated in various non-inflammatory conditions [60], and can be normal in up to 40% of patients with biopsy-proven IgG4-RD [61] and in postpartum IgG4-related hypophysitis [62]. As there does not appear to be a direct relationship between serum IgG4 levels and the number or severity of organs involved in patients with systemic disease, changes in serum IgG4 levels is not necessary for the diagnosis of either comprehensive IgG4-RD or hypophystis [63]. It is also unclear whether serum IgG4 level reflects disease activity because IgG4 itself is not considered a disease driver since it tends to inhibit rather than induce chronic immune activation [64].

If treatment is required, glucocorticoids are the first-line therapy for IgG4-related hypophysitis because the disease responds well to this therapy, with concomitant reductions in serum IgG4 levels [13,17,65,66] that can range from days to 3 months [11,17,62,67]. Treatment should be initiated promptly to revert symptoms and minimize the risk of fibrosis [53,68,69], although there is little evidence of reversal of pituitary function. While there is no consensus for the optimum dose, type, and duration of glucocorticoid therapy, prednisone at a dose of 0.6 mg/kg/day has been used and continued for 1–2 months, with the objective of tapering the dose at a rate of 5 mg/week. Recent studies have reported using low hydrocortisone doses in decreasing serum IgG4 levels and pituitary size [65,66]. Occasionally, stress doses are required to pre-emptively cover for potential adrenal crisis on the day of and the day after surgery. If the disease relapses after glucocorticoid therapy is discontinued or tapered [17,67], continuing at the maintenance dose for an extended period, in some cases exceeding 3 years [70,71], or in combination with rituximab [72], may be required.

We recently reported three patients that presented with non-specific acute symptoms that mimicked pituitary apoplexy, but with normal serum IgG4 levels and no other systemic lesion/s [4]. Because high-dose glucocorticoid therapy was used to treat the acute presenting symptoms of adrenal crisis and mass effects, the diagnosis of IgG4-related hypophysitis was only established after surgery when the histopathologic results became available. These findings of isolated IgG4-related hypophysitis on biopsy with no other systemic lesions have also been reported in Japanese patients [13,58,65,73]. IgG4-RD has also been described in the pediatric population, but usually within the context of autoimmune pancreatitis with other systemic manifestations, such as retroperitoneal fibrosis, sialadenitis, and mediastinal adenopathy [20]. Thus, it is possible that previous cases of IgG4-related hypophysitis may have occurred in younger patients but reported as different entities, or that treatment with high-dose glucocorticoids for co-existing systemic symptoms may have effectively treated the hypophysitis and normalized serum IgG4 levels. Refractory hypophysitis with persistent mass effects not responding to high-dose prednisone or progressive symptom worsening (e.g. visual disturbance and/or severe headache) may require surgery.

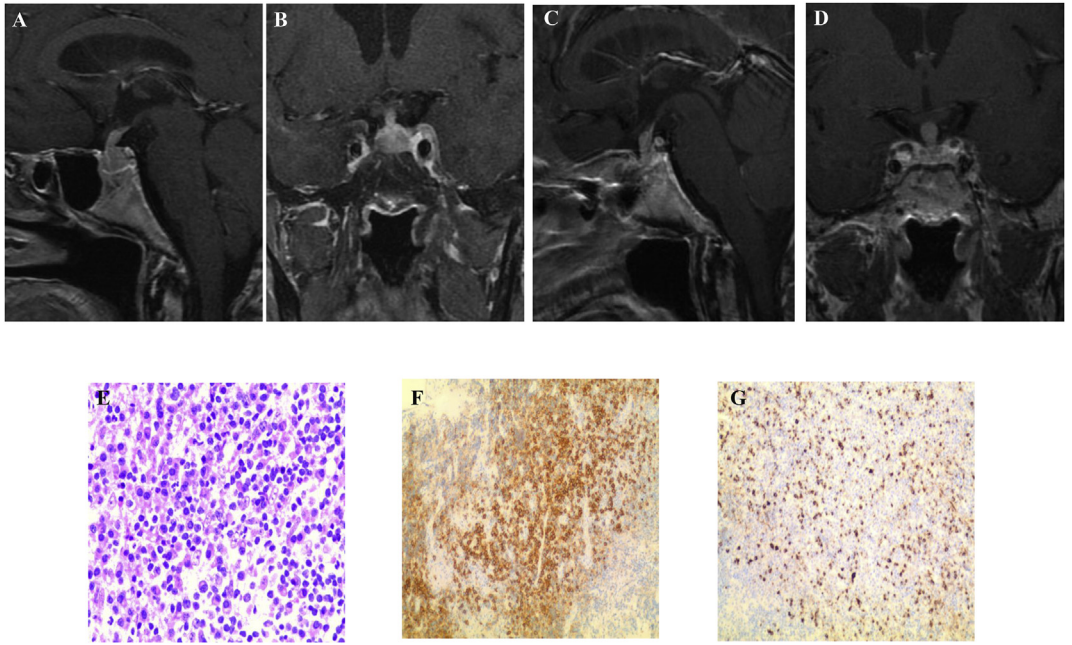

Fig. 4. *MRI*: Pre-operative images (A and B) demonstrate an enlarged pituitary gland with thickening of the stalk. Post-operative images (C and D) show enhancing tissue within the sella, decreased in volume compared to the preoperative examination reflecting post-surgical changes and residual pituitary tissue. Enlarged, avidly-enhancing pituitary stalk is unchanged from the pre-operative images (A and B). *Histopathology*: Hematoxylin and eosin, 400× original magnification demonstrate dense inflammatory lymphoplasmacytic infiltrate that composed of mature plasma cells, histiocytes, lymphocytes and eosinophils, with focal regions of interstitial fibrosis (E). High-power IgG immunostain (100×) demonstrate abundant IgG-positive plasma cells diffusely distributed within the infiltrate (F) and significant number of IgG4-positive cells (number of IgG4-positive cells per high power field is > 200; IgG4/IgG ratio estimated 30–40%) (G). Adapted from Yuen KC et al. [4].

Table 3
Leporati et al. [17] diagnostic criteria for IgG4-related hypophysitis.

Criterion 1: Pituitary histopathology
Mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with >10 IgG4-positive cells per high-power field
Criterion 2: Pituitary MRI
Sellar mass and/or thickened pituitary stalk
Criterion 3: Biopsy-proven involvement in other organs
Association with IgG4-positive lesions in other organs
Criterion 4: Serology
Increased serum IgG4 level (>140 mg/dL)
Criterion 5: Response to glucocorticoids
Decrease in size of the pituitary mass and symptomatic improvement with glucocorticoids
Diagnosis of IgG4-related hypophysitis is established when any of the following is fulfilled:
Criterion 1
Criteria 2 and *3*
Criteria 2, 4, and *5*

Other newly described causes of hypophysitis

Erdheim-Chester disease

Erdheim–Chester disease (ECD) is a rare multisystem non-Langerhans cell form of histiocytosis characterized by infiltration of lipid-laden macrophages and multinucleated giant cells. Xanthomatous or xanthogranulomatous infiltration occurs in the bone, brain, skin, heart, lung, liver and kidney. Long bone pains and symmetric osteosclerotic lesions are suggestive of this disease, which is confirmed by tissue biopsies showing histiocytes with non-Langerhans features. Similar to Langerhans cell histiocytosis, in more than 50% of patients, BRAF V600E mutations are found in the early multipotent hematological precursors or local tissue histiocytes [74]. In a recent French study involving 64 patients with ECD, central DI was reported in 33% of patients with a high rate of concomitant pituitary involvement (91% of patients had partial anterior pituitary deficiency) that persisted after radiographic regression of the disease [75]. In that study, anterior pituitary dysfunction was more frequent than pituitary MRI anomalies (pituitary stalk thickening). FDG-PET/CT imaging has also recently been shown to be helpful in locating the pituitary lesion and other organ involvement [76]. Treatment options for ECD include vemurafenib [77], interferon-α [78], dabrafenib [79], trametinib [79], cobimetinib [80], cladribine [81], sirolimus [82], and glucocorticoids [82].

Anti-Pit-1 antibody syndrome

This syndrome is a recently described clinical entity that causes acquired hypopituitarism [83]. Pit-1 is required for differentiation, proliferation and maintenance of pituitary somatotrophs, lactotrophs, and thyrotrophs. Hence patients present with GH, prolactin and TSH deficiencies with detectable anti-Pit 1 antibodies [84]. The exact pathogenesis is unclear, and it is thought that the aberrant expression of Pit-1 in the thymoma might play a role in the development of this condition [85].

Conclusions

In patients with immune CPI-mediated and lymphocytic hypophysitis associated with pregnancy, the diagnosis may be established with relative confidence. For other causes, because of its heterogeneity, the diagnosis requires the clinician to perform a thorough clinical, laboratory and imaging evaluation for other potential neoplastic lesions, infiltrative diseases, sellar and parasellar tumors, and systemic inflammatory processes. The diagnostic process is challenging because the pathogenesis of some forms of hypophysitis is not fully understood, and clinically validated and reliable serum biomarkers have not yet been identified. Furthermore, in some cases, tissue biopsy may not be feasible.

Acute symptoms such as cranial nerve palsies, severe headache, nausea and vomiting may mimic pituitary apoplexy and adrenal crisis, and it remains unclear if active treatment improves clinical outcomes compared to supportive therapy with high-dose glucocorticoid therapy. Pituitary surgery is reserved for patients with mass effect unresponsive to medical therapy and/or progressive disease. Finally, published studies are largely limited to retrospective analyses that include patients with diverse pathologies and treatment regimens. It is fair to say that hypophysitis, despite the increasing recognition of new causes, remains still a 'fascinoma' to many endocrinologists.

Declaration of interest

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Practice points

- During the acute phase of hypophysitis, emergent assessment of pituitary hormone secretion should be performed, and appropriate management is imperative for any detected endocrinopathies, particularly acute adrenal insufficiency.
- In cases without mass effect, treatment of hypopituitarism, if present, with physiological hormone replacement therapy, and close monitoring are needed as spontaneous resolution of pituitary enlargement over time has been reported.
- Treatment with pharmacological doses of glucocorticoids may be of value in reducing the mass effect, but there is little evidence of its role in facilitating recovery of pituitary function, and conversely, may reduce survival in patients with melanoma.
- Surgery is generally rarely indicated, but may be considered when mass effect is not effectively relieved by glucocorticoid therapy, and when the diagnosis remains questionable and tissue diagnosis is required.
- Endocrine assessment in any patient who is unwell on CPI therapy should be promptly undertaken. If there is any clinical suspicion of adrenal insufficiency, physiological doses of glucocorticoid replacement should be initiated. If there is a clinical suspicion of acute adrenal crisis without mass effect, emergent stress dosing with glucocorticoids should be initiated, while high-dose glucocorticoids could be considered in patients with mass effect.
- In CPI-treated cancer patients, long-term follow-up with a repeat MRI is recommended. Discontinuation of ipilimumab may not be necessary as it did not improve the outcome of hypophysitis or hypophysitis-related hypopituitarism when compared to patients who remained on therapy, and that recovery of pituitary function may occur in some patients that continued ipilimumab.
- Patients with IgG4-related hypophysitis and multi-organ 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.

Research agenda

- Given the lack of data that is constrained by the rarity of the disease, further prospective studies are needed to enhance the understanding of the pathogenesis, diagnosis, and management of hypophysitis, particularly new causes of hypophysitis, as they are increasingly seen in clinical practice.

- Identifying risk factors that predispose to the development of hypophysitis in susceptible individuals could help determine the frequency of monitoring and follow-up.
- Insufficient sensitivity and specificity of currently reported methods prevents recommending measurement of anti-pituitary antibodies as standard of care in the diagnosis of hypophysitis. Although several studies over the years have reported the presence of possible antigens, such as α-enolase [86], secretogrannin II [87], pituitary gland-specific factors (PGSF1a and PGSF2) [88,89] and corticotroph-specific transcriptional factor [90], the exact pathogenicity of these antigens and its implications in the causation of hypophysitis remains unclear. Iwama et al. [91] recently demonstrated the presence of anti-rabphilin-3A antibody in the majority of patients with DI and suspected lymphocytic hypophysitis, suggesting that this might be a potential diagnostic biomarker.
- For immune CPI-mediated hypophysitis, more research is needed for the role of glucocorticoids in the acute setting and its effects on the resolution of endocrinopathies, and oncologic outcomes.
- For IgG4-related hypophysitis, increased description and awareness of the variability of clinical presentation is needed to help clinicians in making the diagnosis.
- The utility of FDG-PET/CT has shown promise in diagnosing IgG4-RD by demonstrating the uptake pattern and multi-organ involvement that may obviate the need of invasive tissue biopsies [92,93].

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