Conducting pituitary care: innovation and standardization in a rare disease

Vries, F. de

10 Hypophysitis: a comprehensive overview

Friso de Vries, Wouter R. van Furth, Nienke R. Biermasz, Alberto M. Pereira

Presse Medicale, 2021

ABSTRACT

Hypophysitis is defined as inflammation of the pituitary gland. It is a heterogeneous condition as it can originate from different parts of the pituitary gland, can be caused by different pathophysiological processes, and can be isolated or the manifestation of a underlying systemic disease. Hypophysitis usually presents with endocrine deficiencies, including diabetes insipidus, with varying patterns. A subset of patients presents with mass effects. The last decades major progress has been made in the understanding of this disease. New forms are now recognized, new diagnostics are being developed, and specific treatments are proposed. This review provides an overview of the current knowledge on hypophysitis using an aetiology-based approach and provides the clinician with a stepwise approach to the patient with (suspected) hypophysitis.

INTRODUCTION

Hypophysitis is the collective diagnosis for inflammatory disorders of the pituitary gland and infundibulum. It usually presents with symptoms that are the consequence of mass effects: hypopituitarism (compression of the pituitary and/or the -stalk) or visual symptoms (compression of the optic chiasm). Most forms of hypophysitis are mediated by auto-immune reactions. However, some disorders classically considered hypophysitis are infections, e.g. with granulomatous infiltration, or neoplastic, e.g. Langerhans cell histiocytosis [1].

Though classic primary hypophysitis is a very rare disease with a reported incidence of 1 per 9 million per year [2], interest in hypophysitis has gained renewed attention as a notorious side-effect of immune checkpoint inhibitor therapies in various cancer treatments. The prevalence of hypophysitis has increased tremendously through the identification of new forms, increased awareness, improved imaging, and as a result of the introduction of immune checkpoint inhibitors [3]. Therefore, the earlier reported incidence is probably an underestimation.

Historically, hypophysitis has been classified according to the focus of inflammation as it correlates with clinical presentation [3]. Adenohypophysitis will result in anterior pituitary hormone deficiency, infundibulo-neurohypophysitis in diabetes insipidus, and panhypohypophysitis in both. However, as the focus of inflammation is not specific for certain diagnoses, this review uses an etiology-based classification: auto-immune, neoplastic, and Immune checkpoint inhibitor-related hypophysitis. We provide an overview of the different disorders causing hypophysitis, and of the diagnostic work-up and treatment of a patient with (suspected) hypophysitis. The focus will be on recent developments in the field.

CLINICAL PRESENTATION

Hypophysitis can be suspected in patients presenting with symptoms of endocrine deficiencies. Most endocrine deficiencies initially present with fatigue, but symptoms may include substantial weight gain or loss, anorexia, bradyphrenia, depression, reduced muscle mass, loss of libido and sexual function, and menstrual disturbances in women. Diabetes insipidus presents with polyuria and polydipsia. Additionally, patients with hypophysitis may present with other symptoms that are the consequence of mass effects. The most common signs and symptoms of mass effects are headache, hyperprolactinemia, and compression of the optic chiasm, potentially causing visual

field deficits, altered color perception and decreased visual acuity [4]. However, a variety of rare presentations has been described in various case reports. With the increase of radiological imaging, hypophysitis may also be suspected in case of an incidental finding in brain MRI.

Many symptoms of hypophysitis also occur in patients with pituitary tumours and pituitary apoplexy. However, the endocrine deficiencies in hypophysitis may be sudden-onset or even have an acute presentation in the case of adrenal insufficiency and more often include diabetes insipidus. Moreover, hypophysitis should be suspected in younger patients, pregnant women or women in the postpartum period, patients diagnosed with a systemic disease that may include hypophysitis, and oncology patients using immune-checkpoint inhibitors. Potential differential diagnoses include pituitary adenoma (with or without apoplexy), craniopharyngioma, Rathke's cleft cyst, meningioma, germinoma, dermoid cyst, and lymphoma. In the post-partum period Sheehan's syndrome is a potential alternative diagnosis.

DIAGNOSTIC WORK-UP

This section will describe a stepwise approach to the patient with suspected hypophysitis (also see Table 1). The first step is to substantiate the suspicion of hypophysitis. The first assessments in the diagnostic work-up of a suspected hypophysitis patient are radiological imaging of the pituitary and hypothalamic region using MRI and a full pituitary hormonal panel for correct assessment of any endocrine deficiencies according to current guidelines [5]. If endocrine deficiencies are diagnosed, hormone replacement therapy should be initiated, especially in case of adrenal and thyroid deficiency and diabetes insipidus [5]. As hypophysitis is a rare and complex disease, we advocate to discuss any patient with (suspected) hypophysitis with an experienced pituitary multidisciplinary team in the early stages of the diagnostic work-up and treatment. Pituitary biopsy should be considered and discussed within this team when a definitive diagnosis is warranted or in case of (severe) mass effects. When biopsy or decompression surgery is performed, histopathology will enable confirmation of a specific diagnosis. According to suspected aetiology, additional laboratory assessments and imaging may be warranted.

General assessments will be discussed in this section. Specific diagnostic work-up and features of different aetiologies will be discussed in the corresponding sections.

Basic diagnostics	☐	Draw blood for electrolytes and a full pituitary hormone panel and perform dynamic tests to assess the corticotropic axis
	☐	Acquire a gadolinium-enhanced pituitary MRI
	☐	In case of chiasm compression, refer to neuro-ophthalmologist for assessment of visual acuity and visual field defects
Initial treatment	☐	Initiate hormone replacement immediately in case of corticotropic or thyrotrophic insufficiency or diabetes insipidus
Discuss	☐	Discuss case with institutional or regional multi-disciplinary team
	☐	Consider surgical decompression in case of visual symptoms
Consider aetiology	☐	In case no biopsy is performed: look for signs of a specific aetiology
	☐	Consider secondary causes and perform appropriate diagnostics (e.g. X-ray and skeletal survey in sarcoidosis)
Treatment	☐	If possible: initiate aetiology-specific treatment
	☐	If no specific aetiology is suspected initiate high-dose glucocorticoid treatment
	☐	In case of non-response: consider other systemic therapies, surgery or radiotherapy
Follow-up	☐	Monitor for recurrence, dependent on initial manifestation with MRI +/- Visual fields. Interval to be discussed in MDT taking all features of disease course into account
	☐	In case of recurrence other systemic therapies or radiotherapy may be considered

Table 1. Basic stepwise approach to the patient with suspected hypophysitis

Laboratory assessment

An early morning complete pituitary and end-organ hormone panel is required for all patients with hypothalamic and/or pituitary lesions. For the diagnosis of secondary adrenal insufficiency and growth-hormone deficiency stimulation tests can be used. For assessment of posterior pituitary function a water deprivation test or measurement of serum copeptin can be performed. Deficiencies should be diagnosed according to current guidelines [5]. The pattern of hormone deficiencies is associated with the focus of the hypophysitis and some aetiologies have more typical deficiency patterns [1]. Water and electrolyte imbalances may be present in case of endocrine deficiencies, most notable hyponatremia in adrenal insufficiency, and dehydration with hypernatremia in severe diabetes insipidus, and should not be overlooked. A full leukocyte differentiation can aid in excluding the differential diagnosis of lymphoma.

Pituitary imaging

As CT-imaging can show no to minimal alterations in hypophysitis, high field, gadolinium-enhanced MRI is the preferred imaging modality. Most typically, a moderately enlarged pituitary gland with symmetrical suprasellar extension with post-contrast homogenous enhancement is seen [6]. When the infundibulum is involved, a thickened non-deviated stalk can be observed and the posterior pituitary bright spot may be absent. However, after the acute phase of inflammation imaging may show an empty sella, which may be the result of tissue atrophy after inflammation.

Distinguishing hypophysitis from other pituitary lesions based on imaging alone is difficult and findings should always be interpreted in the context of the clinical presentation and the medical history. Pituitary stalk thickening is suggestive for inflammation, but is only present in a subset of patients with hypophysitis [6]. Gutenberg et al. developed a scoring system to aid in distinguishing hypophysitis from pituitary adenomas. In this scoring system, an enlarged pituitary stalk, relation to pregnancy, a symmetric lesion, lower pituitary volume, loss of the posterior pituitary bright spot (in case of stalk or posterior pituitary lobe involvement with diabetes insipidus), absence of mucosal thickening, presentation at a young age (<30yrs), and homogenous, medium, or high gadolinium enhancement are more suggestive for hypophysitis than pituitary adenoma (Table 2) [7].

Imaging findings may differ between aetiologies. The most prominent features are generally seen in primary lymphocytic hypophysitis, whereas immune checkpoint inhibitor-related hypophysitis may show mild, non-specific features. Cystic masses can be seen in xanthomatous hypophysitis. The focus of alterations on the MRI correlates well with focus of inflammation and can predict pituitary insufficiency pattern [8]. Malignant disease may show aggressive infiltration of parasellar structures (e.g. both cavernous sinuses).

Features suggestive of hypophysitis	Score	Features suggestive of pituitary adenoma	Score
Enlarged infundibulum	–5	Asymmetrical lesion	3
Related to pregnancy	–4	Pituitary mass volume >6 cm3	2
Loss of the posterior pituitary bright spot	–2	Mucosal swelling	2
Medium to high gadolinium enhancement	–1	Heterogeneous gadolinium enhancement	1

Table 2. Features distinguishing hypophysitis and pituitary adenoma, a score of ≤0 is suggestive of hypophysitis. Adapted from Gutenberg et al.

Considering aetiology

In case no biopsy is performed, additional assessments are necessary to guide the clinician to a more specific diagnosis (also see Table 3). Measures of systemic inflammation, such as ESR, LDH, and IgG-4 levels, can be assessed to guide the clinician towards secondary hypophysitis. Assessment of anti-pituitary antibodies is not routinely recommended. There might be a limited role for this assessment in case of unexplained hypopituitarism, and auto-immune hypophysitis is suspected but imaging and/or biopsy is not a feasible option [9].

(Suspected) aetiology	Possible secondary causes	Additional diagnostics
Lymphocytic hypophysitis	Autoimmune polyendocrine syndrome	Anti-TPO antibodies, antibodies against 21-hydroxylase
	Systemic lupus erythematosus	Anti-nuclear antibodies
	Celiac disease	IgA and IgA tTG
	Anti-Pit1 syndrome	Anti-Pit1 antibodies, mediastinal CT-scan
IgG4-related hypophysitis	Systemic IgG4-related disease	Systemic IgG4-levels, FDG-PET scan
Granulomatous hypophysitis	Sarcoidosis	Chest X-ray, serum ACE-levels, CSF analysis, FDG-PET scan
	Crohn's disease	Faeces calprotectin
	Tuberculosis	Travel history, Chest X-ray, Mantoux test, interferon-γ assay
	Granulomatosis with polyangiitis	ANCA antibodies
Histiocytosis	Systemic Langerhans cell histiocytosis or systemic Erdheim-Chester disease	Skeletal imaging (X-ray or CT-scan), FDG-PET scan

Table 3. Possible secondary causes of hypophysitis and their additional diagnostics

TREATMENT

Symptomatic hyperprolactinemia can be treated with dopamine agonists [10]. Glucocorticoids are still the main treatment for hypophysitis [3]. Other immune-modulating drugs have been proposed, such as azathioprine [11-16], infliximab [17-19], and rituximab [13, 18, 20-28]. When mass effects do not subside with anti-inflammatory drugs or when a histological diagnosis is necessary, surgical treatment may be warranted [3, 29]. Pituitary surgery is a highly specialized procedure and should preferably be performed in a high-volume centre to reduce peri-operative morbidity [30]. In case of recurrence or uncontrolled disease, surgery and radiotherapy may be considered.

Mass effects usually disappear or improve with tumour control through drugs or surgery [31-33]. Even though hypopituitarism may recover in some, it often persists after treatment [32, 33]. Responsiveness to glucocorticoids may be predicted by the presence of anti-pituitary antibodies [31]. Presentation with diabetes insipidus has been reported as a predictor of good [31], as well as poor response to glucocorticoid treatment [34]. Recurrences are common following surgical as well as glucocorticoid therapy [32, 35].

Follow-up should consist of assessment of recurrence and pituitary deficiencies. We recommend to routinely draw blood for a full pituitary hormone panel and perform

pituitary MRI. Interval of follow-up assessments should be adjusted to disease aggressiveness and likelihood of recurrence.

AUTO-IMMUNE HYPOPHYSITIS

All types of auto-immune hypophysitis may occur in isolated form, in which case they are considered primary hypophysitis, or in concurrence with a systemic disease, in which case they are considered secondary. This section will describe specific sign and symptoms, aetiology, related diseases, diagnostic findings, and management suggestions for each subtype of auto-immune hypophysitis.

Lymphocytic hypophysitis

The most well-known and common form of primary hypophysitis is lymphocytic hypophysitis, first reported over a century ago. It has an estimated incidence of 1 in 9 million per year, which is probably an underestimation due to misdiagnosis [9, 29]. It occurs more frequently in female patients and with a higher incidence in pregnancy and post-partum period [29].

In the acute inflammatory stage patients can present with classical symptoms of hypophysitis, such as headache and mass effects as a result of pituitary oedema. When pituitary oedema or fibrosis occurs, pituitary deficiencies, most typically gonadotrope, and ultimately panhypopituitarism can develop [29]. Lymphocytic hypophysitis can originate from anywhere in the pituitary and deficiencies are dependent on this focus. Imaging shows typical signs of hypophysitis (figure 1a) [6]. When imaging is inconclusive, but a suspicion of lymphocytic hypophysitis remains, assessment of anti-pituitary antibodies can aid diagnosis [3]. When a biopsy in performed, lymphocytic hypophysitis is characterised by massive infiltration of lymphocytes, plasma cells and macrophages [1].

In contrast to Sheehan's syndrome, lymphocytic hypophysitis can occur anytime during pregnancy and postpartum and should be suspected in women with post-partum endocrine deficiencies without the occurrence substantial blood loss or hypotension during partus. Post-partum lymphocytic hypophysitis is associated with postpartum thyroiditis, in which case anti-TPO antibodies can be detected in the patient's serum [36].

Treatment usually consists of high-dose glucocorticoid treatment. In case of refractory or recurrent disease other immunosuppressive drugs may be used. In case of visual symptoms or necessity of histology, a surgical biopsy and decompression of the optic

chiasm may be performed. As radiotherapy often leads to iatrogenic hypopituitarism this should be reserved for as a last resort [37].

Hypophysitis is associated with multiple other auto-immune disorders, sometimes of the endocrine glands, such as auto-immune thyroiditis, constituting an autoimmune polyendocrine syndrome (APS). It most typically occurs in APS type 1 (with Addison's disease and hypoparathyroidism) and 3 (with type 1 diabetes mellitus), but can also occur in APS type 2 and 4 [9]. Other associated systemic inflammatory disorders are systemic lupus erythematosus, and celiac disease. A central role for activated T-cells has been proposed [1]. In lymphocytic hypophitis, the presence of auto-antibodies to various proteins indigenous to the pituitary in lymphocytic hypophysitis was observed [38] of which anti-rhabphilin may be used as a biomarker [39]. As Rhabphilin-3A is only found in the neuropituitary tissue, it is only a biomarker for hypophisitis which has a focus in the posterior pituitary gland or infundibulum [39, 40]. Moreover, an animal model of continuous generation and proliferation of autoreactive T-cells and generation of autoreactive B-cells within the pituitary gland expressing IFN-γ and IL-17, is associated with auto-immune disease [41]. HLA-DQ8 is associated with lymphocytic hypophysitis in contrast to iatrogenic hypophysitis and other sellar masses [42].

A specific form of lymphocytic hypophysitis is the Anti-Pit1 syndrome that is mediated by cytotoxic T-cells [43-45]. It is characterized by the presence of circulating antibodies targeted to pituitary-specific transcription factor-1 (Pit-1), which is expressed in the somatotropic, lactotrophic and thyrotropic cells of the pituitary. As a result, patients present with growth hormone, prolactin and thyroid stimulating hormone deficiency, while the corticotropic axis and the posterior pituitary gland are spared [43]. The syndrome is associated with thymomas, though cases without a thymoma have also been reported [46]. Diagnosis may be set when a patient presents with acquired growth hormone, prolactin, and thyroid stimulating hormone deficiencies without deficiencies of other pituitary axes, and circulating anti-PIT-1 antibodies, or PIT-1-reactive cytotoxic T lymphocytes are found [43].

IgG4-related hypophysitis

IgG4-related hypophysitis can present as an isolated hypophysitis in approximately 40% of affected patients or with other systemic manifestations of IgG4-related disease, most often manifesting in the lymph nodes, lung, retroperitoneum, kidney, submandibular glands, pancreas, and lacrimal glands [47, 48]. It usually occurs in older patients and more often in males than in females [47-49], however, isolated IgG4-related hypophysitis is more common in females [47, 48]. It is the second most common form of primary hypophysitis comprising 30% of all hypophysitis cases [29, 50, 51]. Patients present

with usual symptoms of hypophysitis: headache, asthenia, mass effects and symptoms of hypopituitarism [52]. Anterior panhypopituitarism and DI are relatively common in IgG4-related hypophysitis compared to other forms. Around 40% of patients present with DI and around 50% develop panhypopituitarism. The most frequently affected anterior pituitary axis is the gonadotropic, followed by the corticotropic and thyrotropic axes [48, 52]. Imaging is not able to distinguish this type of hypophysitis from other types (figure 1b).

A pituitary biopsy showing infiltration of IgG4-positive plasma cells will confirm the diagnosis. However, diagnosis can also be established in case of a suspected pituitary lesion on MRI and a biopsy-proven IgG4-lesion in a different organ. A third possibility for establishing diagnosis is a suspected pituitary lesion on MRI, elevated systemic IgG4-levels (>140mg/dL), and clinical and radiological response to glucocorticoid treatment [53]. Bernreuther et al. analysed cases earlier diagnosed of lymphocytic hypophysitis showed that 40% fulfilled the criteria of IgG4-related hypophysitis, and the prevalence of IgG4-related hypophysitis may be underestimated [54]. FDG-PET imaging can be useful to differentiate IgG4-related hypophysitis from other forms and to localize other involved organs [6].

A recent guideline on IgG4-related disease advises initial treatment with high dose glucocorticoids (prednisone 30-40mg/day), with subsequent slow tapering to prevent recurrence. In patients with multiorgan involvement, long-term therapy may be warranted [20]. As this is mainly a plasma cell-medicated aetiology, the anti-CD-20 antibody rituximab may be a viable alternative when glucocorticoids are ineffective [20, 21].

Granulomatous hypophysitis

Granulomatous hypophysitis is a very rare form of hypophysitis with less than 100 reported cases in literature [55]. It seems to occur more frequently in females than in males and an association with the postpartum period has been reported [56]. It may have a more aggressive clinical course and visual symptoms are relatively frequent. Other symptoms correspond with those of other forms of hypophysitis: nausea, headache [55]. The most affected pituitary axis is the gonadotropic axis[35]. Pituitary imaging shows general signs of hypophysitis and does not aid in distinguishing granulomatous from lymphocytic or IgG4-related hypophysitis (figure 1c). Biopsy may show giant cells, most typically multinucleate. It can also show infiltration of lymphocytes, macrophages, and plasma cells [55].

As with other forms of hypophysitis, primary treatment is often with high-dose glucocorticoids. However, treatment response in poorer than in other forms of hypophysitis. As visual symptoms are relatively common, surgical resection is performed more often.

Granulomatous hypophysitis may occur as primary disease or secondary to systemic granulomatous disease. It has been reported in the context of sarcoidosis, Crohn's disease, tuberculosis, and granulomatosis with polyangiitis [3]. In case granulomatous hypophysitis is suspected, it may be useful to screen for the presence of these diseases, most typically starting with imaging of the thorax and measurement of circulating autoantibodies.

Xanthomatous hypophysitis

Xanthomatous hypophysitis was first described in 1993 by Folkerth et al. [57]. It is more common in females than in males an predominantly occurs in younger patients (<40 years) [58, 59]. Clinical presentation shows typical sings of hypophysitis: headache, diabetes insipidus and sings of anterior pituitary deficiencies [35, 59]. Disease course may be elongated and mild, with relatively few visual symptoms [35, 58]. On sellar imaging, xanthomatous hypophysitis shows as a cystic sellar mass with peripheral contrast-enhancement [6]. As response to glucocorticoids is reported to be poor, surgical resection is performed more often than in other forms of hypophysitis [60]. As with hypophysitis in general, symptoms of mass effects usually disappear after treatment, but hypopituitarism often persist [61, 62].

It is speculated that xanthomatous hypophysitis constitutes a spectrum of xanthomatous inflammation together with xanthogranulomatous hypophysitis and pituitary xanthogranulomas, with multiple cases showing foci fitting more than one of these diagnoses [59]. Histologically, xanthomatous hypophysitis is characterised by infiltration of foamy xanthoma cells and lymphocytes, which probably results from macrophage activation [59, 60]. Immunostaining may show CD68 as a marker for macrophage activation [58, 60]. Xanthogranulomatous hypophysitis additionally shows infiltration with multinucleated giant cells and epitheliod histiocytes [63]. Xanthogranulomas can show cholesterol clefts and lymphoplasmacytic infiltrates, with hemosiderin deposits, fibrosis, giant cells, eosinophilic granular necrotic debris, and macrophages [64]. Rupture of a sellar cysts, such as Rathke's Cleft Cysts, arachnoid cysts, or adamantinomatous craniopharyngiomas, are associated with the development of xanthomatous lesions of the pituitary gland [59, 63].

Necrotizing hypophysitis

Necrotizing hypophysitis is extremely rare, with only 4 reported cases to date. Whether this is a distinct clinical entity is still a topic for debate, also because the underlying pathophysiology remains unelucidated. Clinical presentation does not differ from other forms of hypophysitis, but may be acute [65]. Clinically, symptoms may resemble pituitary apoplexy. However, pituitary imaging will usually distinguish between these two diagnoses as necrotizing hypophysitis shows usual signs of hypophysitis and pituitary apoplexy is usually visible as a (large) heterogeneously enhancing mass. Imaging does not distinguish between necrotizing, lymphocytic and IgG4-related hypophysitis [6]. Pituitary biopsy shows mononuclear infiltration with necrosis of the pituitary tissue [65].

NEOPLASTIC HYPOPHYSITIS

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LHCH) is a neoplastic disorder that was previously considered to be inflammatory [50, 66, 67]. Presently, it is defined as an inflammatory myeloid neoplasm, characterized by the accumulation of Langerhans cell histiocytosis cells [68]. Though named after skin Langerhans cells, Langerhans cell histiocytosis cells probably derive from myeloid dendritic cells [68]. It is very rare with an incidence of 1-2 cases per million per year and usually presents in childhood [50]. A wide variety of organs can be involved, including lungs, bones, skin, and the central nervous system. The hypothalamic-pituitary tract is the most common localization within the central nervous system localization, and may even be a solitary expression site [68].

When the pituitary is involved, LHCH usually presents with diabetes insipidus, though anterior hypopituitarism can also occur. Diabetes insipidus occurs in 12% of children and 30% of adults with Langerhans cell histiocytosis [50, 69]. The most commonly affected anterior pituitary hormone axes are the somatotropic and gonadotropic, affecting 53-67%, and 53-58% of patients with Langerhans cell histiocytosis, and DI [69]. Pituitary imaging most typically shows pituitary stalk thickening and loss of the posterior pituitary bright spot (figure 1d) [70]. As the lungs and bones are commonly affected sites for Langerhans cell histiocytosis, imaging of the lungs and skeleton via X-ray, CT or PET is advocated for assessment of other (active) sites when this diagnosis is considered [71]. To confirm diagnosis, a biopsy is necessary, most preferably from a less invasive site than the pituitary, if possible [71]. When the pituitary is involved, systemic treatment with chemotherapy, such as vinblastine, is advised aside from local therapy. Local therapy may consist of surgery (in case of biopsy) or radiation therapy [71]. Patients with BRAF(V600E) mutation are more often treatment-resistant for systemic therapy

and have a higher reactivation rate [72]. Endocrine deficiencies seldom recover after treatment [70].

Erdheim-Chester disease

Erdheim-Chester disease is a form of histiocytosis, defined as non-Langerhans cell, with the hall-mark of carrying the BRAF(V600E) mutation [73]. Aside from lesions with histiocytosis, it can cause xanthomatous lesions [74], and it can involve multiple organs [75]. Pituitary involvement usually presents with symptoms of anterior pituitary hormone deficiency, though one third of patients also experiences diabetes insipidus [74]. Similar to Langerhans cell histiocytosis, Erdheim-Chester disease of the pituitary should be treated with systemic (chemo)therapy [75].

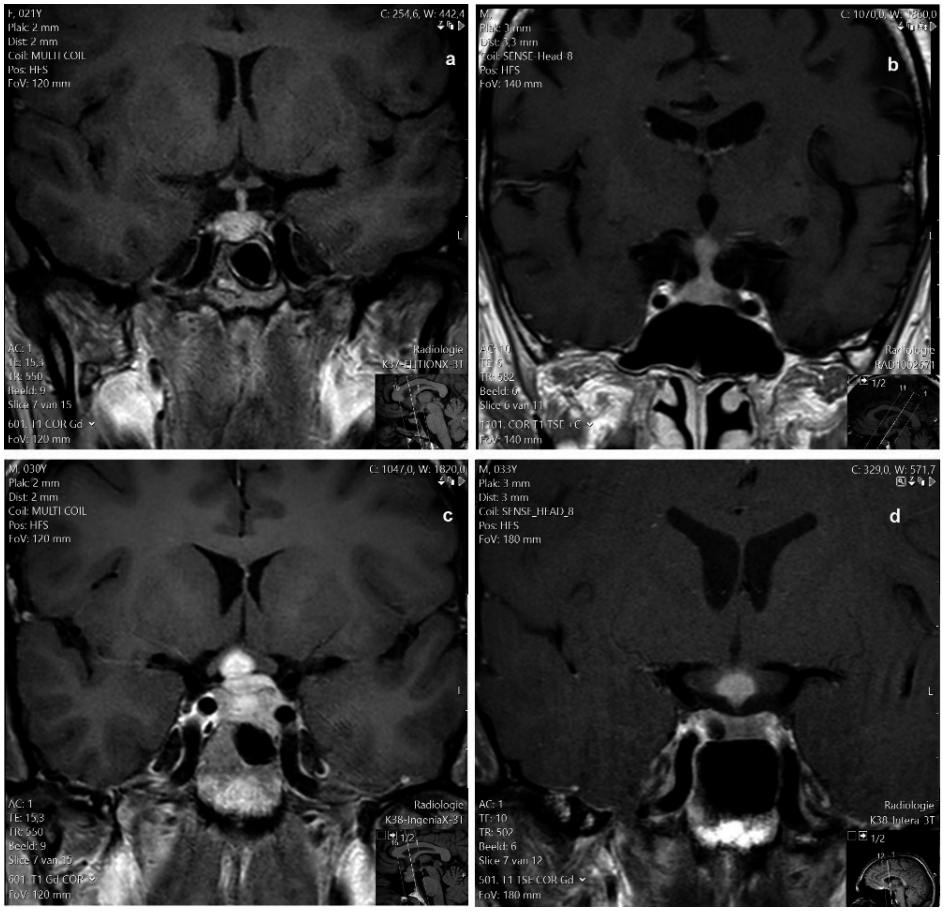

Figure 1. MRI images of 4 types of hypophysitis, all showing typical pituitary stalk thickening. a: lymphocytic hypophysitis, b: IgG4-related hypophysitis, c: granulomatous hypophysitis in the context of neurosarcoidosis, d: Langerhans cell histiocytosis (this image also shows a small cystic pituitary adenoma)

IMMUNE CHECKPOINT INHIBITOR-RELATED HYPOPHYSITIS

With the introduction of ipilimumab (CTLA-4 antibody) in 2011, a new form of hypophysitis emerged into clinical practice: the immune checkpoint inhibitor-related hypophysitis. In the following years, more immune checkpoint inhibitors have been introduced: targeting the PD-1 receptor and its ligand PD-L1 [76].

Ipilimumab is a monoclonal antibody against the CTLA-4 receptor that is involved in immunosuppressive pathways. By activating the CTL-4 receptor, tumor cells can down-regulate activation of T-lymphocytes and this effect can be abrogated by administering ipilimumab, re-enhancing immune responses [1, 76, 77]. Binding of PD-1 to PD-L1 and PD-L2, which can be expressed by tumour cells, inhibits T-cell activation, proliferation and pro-inflammatory cytokine production, resulting in reduced immune activation. Antagonists to PD-1 and PD-L1 block this pathway and, consequently, enhance immune response [76]. Though these antibodies are highly effective oncologic agents, patients may also experience the negative effects of enhancing immunity in the form of iatrogenic inflammatory disease. Why the pituitary gland is one of the most common affected sites of this iatrogenic inflammation remains yet to be fully elucidated. For CTLA-4 Abs, proposed pathways are pituitary expression of CTLA-4 antigens activating the classic complement pathway, direct binding of CTLA-4 Ab to pituitary cells, and development of anti-pituitary antibodies [1, 77]. A recent autopsy study found dominant infiltration of type 2 macrophages aside from T-lymphocytes in affected pituitaries, suggesting over-activation of these macrophages in uncontrolled immune response in these patients [78]. In a Japanese study HLA-DR15, associated with auto-immune disease, was more prevalent in patients than in controls [79]. No specific explanations for the pathogenesis of PD- (L)1- related hypophysitis have been substantiated. However, as PD-(L)1 Abs are IgG4, pathogenesis may resemble that of IgG4-related hypophysitis [1].

A recent meta-analysis including data from 160 trials involving 40 432 participants reported an incidence rate of . 3.25% (95% CI, 2.15%-4.51%) for hypophysitis [80]. Hypophysitis occurs more frequently in males than in females [81, 82], at older age [81], and the incidence is higher in patients using CTLA-4 Abs than those using PD-(L)1 Abs [80, 83]. The difference in prevalence between sexes might be explained by the effects of sex hormones on the immune system. However, other immune checkpoint inhibitor-related auto-immune disorders occur more frequently in females [82]. Median time of onset is 9 weeks after treatment initiation (during the third cycle), though it can occur from the first cycle to 19 months after initiation [84]. Screening for hypopituitarism during treatment with immune checkpoint inhibitors is now recommended in many guidelines. A

fall in TSH [76, 85] or T4 and TSH index [86] may precede hypopituitarism. In some cases where patients were screened using MRI, structural imaging abnormalities showing typical signs of hypophysitis preceded symptoms. Immune-checkpoint inhibitor-related hypophysitis presents with the same symptoms as any other form of hypophysitis. However, endocrine deficiencies mainly involve anterior pituitary hormone deficiencies, especially of the thyrotrope, corticotrope and gonadotroph axes. Hypophysitis should be suspected in patients on immune checkpoint inhibitor therapy with acute onset headache or symptoms of endocrine deficiency. Headache is reported to be the presenting symptom more often in patients on CTLA-4 Abs than on PD-(L)1 Abs [83]. MRI can be used to ratify suspicion of hypophysitis, showing a poorly enhanced lesion [87, 88], distinguishing hypophysitis from pituitary metastases and other pituitary lesions.

Treatment consists of hormone replacement of deficient axes. In severe cases, abrogation of immune checkpoint inhibitor therapy and administering high-dose glucocorticoids may be considered. As hypocortisolism can be life-threatening, glucocorticoid replacement should be initiated in case sufficient cortisol secretion is uncertain. Hypopituitarism is mostly permanent, but restoration of pituitary hormone secretion has been reported in some cases [87, 89].

CONCLUSION

Though hypophysitis has been reported on for a century, the last decades large progressions have been made in the knowledge of its pathophysiology. This is mainly due to the increased prevalence of hypophysitis with the newly described aetiologies. New types of hypophysitis are now recognized and specific treatments based on the underlying pathophysiology are proposed. With expanding understanding, new biomarkers or diagnostics and therapeutic drugs can be developed to aid patient and clinician in a more accurate diagnosis and treatment. As this is still a rare disease, evidence is mainly based on small observational studies. Therefore, we call on experts-in-the-field to collaborate on larger trials, for example through rare disease networks, to gain more insight and evidence in this heterogeneous disease. Diagnosis and treatment should follow a stepwise approach and an expert multidisciplinary team on pituitary disease should be consulted as soon as possible to optimize disease management and outcomes. Aside from biochemical outcome, potential loss of quality of life of hypophysitis patients should not be overlooked.

REFERENCES

1. Takahashi Y. MECHANISMS IN ENDOCRINOLOGY: Autoimmune hypopituitarism: novel mechanistic insights. Eur J Endocrinol. 2020;182(4):R59-r66.
2. Caturegli P, Newschaffer C, Olivi A, et al. Autoimmune Hypophysitis. Endocr Rev. 2005;26(5):599-614.
3. Joshi MN, Whitelaw BC, Carroll PV. MECHANISMS IN ENDOCRINOLOGY: Hypophysitis: diagnosis and treatment. Eur J Endocrinol. 2018;179(3):R151-r63.
4. Angelousi A, Cohen C, Sosa S, et al. Clinical, Endocrine and Imaging Characteristics of Patients with Primary Hypophysitis. Horm Metab Res. 2018;50(4):296-302.
5. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(11):3888-921.
6. Caranci F, Leone G, Ponsiglione A, et al. Imaging findings in hypophysitis: a review. Radiol Med. 2020;125(3):319-28.
7. Gutenberg A, Larsen J, Lupi I, et al. A radiologic score to distinguish autoimmune hypophysitis from nonsecreting pituitary adenoma preoperatively. AJNR Am J Neuroradiol. 2009;30(9):1766-72.
8. Tartaglione T, Chiloiro S, Laino ME, et al. Neuro-radiological features can predict hypopituitarism in primary autoimmune hypophysitis. Pituitary. 2018;21(4):414-24.
9. Bellastella G, Maiorino MI, Bizzarro A, et al. Revisitation of autoimmune hypophysitis: knowledge and uncertainties on pathophysiological and clinical aspects. Pituitary. 2016;19(6):625-42.
10. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273-88.
11. Caputo C, Bazargan A, McKelvie PA, et al. Hypophysitis due to IgG4-related disease responding to treatment with azathioprine: an alternative to corticosteroid therapy. Pituitary. 2014;17(3):251-6.
12. Curtò L, Torre ML, Cotta OR, et al. Lymphocytic hypophysitis: differential diagnosis and effects of high-dose pulse steroids, followed by azathioprine, on the pituitary mass and endocrine abnormalities--report of a case and literature review. ScientificWorldJournal. 2010;10:126-34.
13. Gendreitzig P, Honegger J, Quinkler M. Granulomatous hypophysitis causing compression of the internal carotid arteries reversible with azathioprine and rituximab treatment. Pituitary. 2020;23(2):103-12.
14. Lecube A, Francisco G, Rodríguez D, et al. Lymphocytic hypophysitis successfully treated with azathioprine: first case report. J Neurol Neurosurg Psychiatry. 2003;74(11):1581-3.
15. Lupi I, Manetti L, Raffaelli V, et al. Diagnosis and treatment of autoimmune hypophysitis: a short review. J Endocrinol Invest. 2011;34(8):e245-52.
16. Papanastasiou L, Pappa T, Tsiavos V, et al. Azathioprine as an alternative treatment in primary hypophysitis. Pituitary. 2011;14(1):16-22.
17. Force BK, Vogel TP, Nguyen DM, et al. A Remarkable Response of Granulomatous Hypophysitis to Infliximab in a Patient With a Background of Crohn's Disease-A Case Report. Front Endocrinol (Lausanne). 2020;11:350.
18. Xu C, Ricciuti A, Caturegli P, et al. Autoimmune lymphocytic hypophysitis in association with autoimmune eye disease and sequential treatment with infliximab and rituximab. Pituitary. 2015;18(4):441-7.
19. Hryniewicki AT, Wang C, Shatsky RA, et al. Management of Immune Checkpoint Inhibitor Toxicities: A Review and Clinical Guideline for Emergency Physicians. J Emerg Med. 2018;55(4):489-502.

20. Khosroshahi A, Wallace ZS, Crowe JL, et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. Arthritis Rheumatol. 2015;67(7):1688-99.
21. Boharoon H, Tomlinson J, Limback-Stanic C, et al. A Case Series of Patients with Isolated IgG4-related Hypophysitis Treated with Rituximab. J Endocr Soc. 2020;4(6):bvaa048.
22. Bullock DR, Miller BS, Clark HB, et al. Rituximab treatment for isolated IgG4-related hypophysitis in a teenage female. Endocrinol Diabetes Metab Case Rep. 2018;2018.
23. De Bellis A, Colella C, Bellastella G, et al. Rituximab-induced remission of autoimmune hypophysitis and primary immune thrombocytopenia in a patient with autoimmune polyendocrine syndrome type 4. Expert Rev Endocrinol Metab. 2014;9(4):313-7.
24. Gu WJ, Zhang Q, Zhu J, et al. Rituximab was used to treat recurrent IgG4-related hypophysitis with ophthalmopathy as the initial presentation: A case report and literature review. Medicine (Baltimore). 2017;96(24):e6934.
25. Lin M, Tsang V, Brewer J, et al. Infiltrative lymphocytic hypophysitis successfully treated with rituximab and mycophenolate mofetil. Endocrinol Diabetes Metab Case Rep. 2020;2020.
26. Ramakrishna MP, Arun CS, Pavithran PV, et al. Hypophysitis in granulomatosis with polyangiitis: rare presentation of a multisystem disease. J R Coll Physicians Edinb. 2020;50(3):287-90.
27. Schreckinger M, Francis T, Rajah G, et al. Novel strategy to treat a case of recurrent lymphocytic hypophysitis using rituximab. J Neurosurg. 2012;116(6):1318-23.
28. Vauchot F, Bourdon A, Hay B, et al. Therapeutic Response to Rituximab in IgG4-Related Hypophysitis Evidenced on 18F-FDG PET and MRI. Clin Nucl Med. 2019;44(5):e362-e3.
29. Caturegli P, Lupi I, Landek-Salgado M, et al. Pituitary autoimmunity: 30 years later. Autoimmun Rev. 2008;7(8):631-7.
30. Honegger J, Grimm F. The experience with transsphenoidal surgery and its importance to outcomes. Pituitary. 2018;21(5):545-55.
31. Chiloiro S, Tartaglione T, Capoluongo ED, et al. Hypophysitis Outcome and Factors Predicting Responsiveness to Glucocorticoid Therapy: A Prospective and Double-Arm Study. J Clin Endocrinol Metab. 2018;103(10):3877-89.
32. Honegger J, Buchfelder M, Schlaffer S, et al. Treatment of Primary Hypophysitis in Germany. J Clin Endocrinol Metab. 2015;100(9):3460-9.
33. Amereller F, Küppers AM, Schilbach K, et al. Clinical Characteristics of Primary Hypophysitis - A Single-Centre Series of 60 Cases. Exp Clin Endocrinol Diabetes. 2021;129(3):234-40.
34. Lupi I, Cosottini M, Caturegli P, et al. Diabetes insipidus is an unfavorable prognostic factor for response to glucocorticoids in patients with autoimmune hypophysitis. Eur J Endocrinol. 2017;177(2):127-35.
35. Gutenberg A, Hans V, Puchner MJA, et al. Primary hypophysitis: clinical-pathological correlations. European Journal of Endocrinology eur j endocrinol. 2006;155(1):101-7.
36. Di Bari F, Granese R, Le Donne M, et al. Autoimmune Abnormalities of Postpartum Thyroid Diseases. Front Endocrinol (Lausanne). 2017;8:166.
37. Angelousi A, Alexandraki K, Tsoli M, et al. Hypophysitis (Including IgG4 and Immunotherapy). Neuroendocrinology. 2020;110(9-10):822-35.
38. Prete A, Salvatori R. Hypophysitis. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000.
39. Iwama S, Arima H. Anti-pituitary antibodies as a marker of autoimmunity in pituitary glands. Endocr J. 2020;67(11):1077-83.
40. Yasuda Y, Iwama S, Kiyota A, et al. Critical role of rabphilin-3A in the pathophysiology of experimental lymphocytic neurohypophysitis. J Pathol. 2018;244(4):469-78.

41. Lin H-H, Gutenberg A, Chen T-Y, et al. In Situ Activation of Pituitary-Infiltrating T Lymphocytes in Autoimmune Hypophysitis. Sci Rep. 2017;7(1):43492.
42. Heaney AP, Sumerel B, Rajalingam R, et al. HLA Markers DQ8 and DR53 Are Associated With Lymphocytic Hypophysitis and May Aid in Differential Diagnosis. The Journal of Clinical Endocrinology & Metabolism. 2015;100(11):4092-7.
43. Yamamoto M, Iguchi G, Takeno R, et al. Adult combined GH, prolactin, and TSH deficiency associated with circulating PIT-1 antibody in humans. J Clin Invest. 2011;121(1):113-9.
44. Yamamoto M, Iguchi G, Bando H, et al. Autoimmune Pituitary Disease: New Concepts With Clinical Implications. Endocr Rev. 2020;41(2).
45. Kanie K, Bando H, Iguchi G, et al. Pathogenesis of Anti-PIT-1 Antibody Syndrome: PIT-1 Presentation by HLA Class I on Anterior Pituitary Cells. J Endocr Soc. 2019;3(11):1969-78.
46. Kanie K, Iguchi G, Inuzuka M, et al. Two Cases of anti-PIT-1 Hypophysitis Exhibited as a Form of Paraneoplastic Syndrome not Associated With Thymoma. J Endocr Soc. 2021;5(3):bvaa194.
47. Shikuma J, Kan K, Ito R, et al. Critical review of IgG4-related hypophysitis. Pituitary. 2017;20(2):282-91.
48. Li Y, Gao H, Li Z, et al. Clinical Characteristics of 76 Patients with IgG4-Related Hypophysitis: A Systematic Literature Review. Int J Endocrinol. 2019;2019:5382640.
49. Iseda I, Hida K, Tone A, et al. Prednisolone markedly reduced serum IgG4 levels along with the improvement of pituitary mass and anterior pituitary function in a patient with IgG4-related infundibulo-hypophysitis. Endocr J. 2014;61(2):195-203.
50. Makras P, Kaltsas G. Langerhans cell histiocytosis and pituitary function. Endocrine. 2015;48(3):728-9.
51. Bando H, Iguchi G, Fukuoka 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. 2014;170(2):161-72.
52. Lojou M, Bonneville JF, Ebbo M, et al. IgG4 hypophysitis: Diagnosis and management. Presse Med. 2020;49(1):104016.
53. Leporati P, Landek-Salgado MA, Lupi I, et al. IgG4-Related Hypophysitis: A New Addition to the Hypophysitis Spectrum. The Journal of Clinical Endocrinology & Metabolism. 2011;96(7):1971-80.
54. Bernreuther C, Illies C, Flitsch J, et al. IgG4-related hypophysitis is highly prevalent among cases of histologically confirmed hypophysitis. Brain Pathol. 2017;27(6):839-45.
55. Hunn BHM, Martin WG, Simpson S, et al. Idiopathic granulomatous hypophysitis: a systematic review of 82 cases in the literature. Pituitary. 2014;17(4):357-65.
56. Joneja U, Hooper DC, Evans JJ, et al. Postpartum Granulomatous Hypophysitis: A Case Study, Review of the Literature, and Discussion of Pathogenesis. Case Reports in Pathology. 2016;2016:7510323.
57. Folkerth RD, Price DL, Jr., Schwartz M, et al. Xanthomatous hypophysitis. Am J Surg Pathol. 1998;22(6):736-41.
58. Aste L, Bellinzona M, Meleddu V, et al. Xanthomatous Hypophysitis Mimicking a Pituitary Adenoma: Case Report and Review of the Literature. J Oncol. 2010;2010:195323.
59. Kleinschmidt-DeMasters BK, Lillehei KO, Hankinson TC. Review of xanthomatous lesions of the sella. Brain Pathol. 2017;27(3):377-95.
60. Hanna B, Li YM, Beutler T, et al. Xanthomatous hypophysitis. J Clin Neurosci. 2015;22(7):1091-7.
61. Burt MG, Morey AL, Turner JJ, et al. Xanthomatous pituitary lesions: a report of two cases and review of the literature. Pituitary. 2003;6(3):161-8.

62. Gutenberg A, Buslei R, Fahlbusch R, et al. Immunopathology of primary hypophysitis: implications for pathogenesis. Am J Surg Pathol. 2005;29(3):329-38.
63. Tashiro T, Sano T, Xu B, et al. Spectrum of different types of hypophysitis: a clinicopathologic study of hypophysitis in 31 cases. Endocr Pathol. 2002;13(3):183-95.
64. Paulus W, Honegger J, Keyvani K, et al. Xanthogranuloma of the sellar region: a clinicopathological entity different from adamantinomatous craniopharyngioma. Acta Neuropathol. 1999;97(4):377-82.
65. Gutenberg A, Caturegli P, Metz I, et al. Necrotizing infundibulo-hypophysitis: an entity too rare to be true? Pituitary. 2012;15(2):202-8.
66. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010;116(11):1919-23.
67. Badalian-Very G, Vergilio JA, Fleming M, et al. Pathogenesis of Langerhans cell histiocytosis. Annu Rev Pathol. 2013;8:1-20.
68. Kobayashi M, Tojo A. Langerhans cell histiocytosis in adults: Advances in pathophysiology and treatment. Cancer Sci. 2018;109(12):3707-13.
69. Makras P, Alexandraki KI, Chrousos GP, et al. Endocrine manifestations in Langerhans cell histiocytosis. Trends Endocrinol Metab. 2007;18(6):252-7.
70. Makras P, Samara C, Antoniou M, et al. Evolving radiological features of hypothalamo-pituitary lesions in adult patients with Langerhans cell histiocytosis (LCH). Neuroradiology. 2006;48(1):37-44.
71. Girschikofsky M, Arico M, Castillo D, et al. Management of adult patients with Langerhans cell histiocytosis: recommendations from an expert panel on behalf of Euro-Histio-Net. Orphanet J Rare Dis. 2013;8:72.
72. Héritier S, Emile JF, Barkaoui MA, et al. BRAF Mutation Correlates With High-Risk Langerhans Cell Histiocytosis and Increased Resistance to First-Line Therapy. J Clin Oncol. 2016;34(25):3023-30.
73. Milne P, Bigley V, Bacon CM, et al. Hematopoietic origin of Langerhans cell histiocytosis and Erdheim-Chester disease in adults. Blood. 2017;130(2):167-75.
74. Courtillot C, Laugier Robiolle S, Cohen Aubart F, et al. Endocrine Manifestations in a Monocentric Cohort of 64 Patients With Erdheim-Chester Disease. J Clin Endocrinol Metab. 2016;101(1):305-13.
75. Yuen KCJ, Popovic V, Trainer PJ. New causes of hypophysitis. Best Pract Res Clin Endocrinol Metab. 2019;33(2):101276.
76. Albarel F, Castinetti F, Brue T. MANAGEMENT OF ENDOCRINE DISEASE: Immune check point inhibitors-induced hypophysitis. Eur J Endocrinol. 2019;181(3):R107-r18.
77. Iwama S, De Remigis A, Callahan MK, et al. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med. 2014;6(230):230ra45.
78. Mihic-Probst D, Reinehr M, Dettwiler S, et al. The role of macrophages type 2 and T-regs in immune checkpoint inhibitor related adverse events. Immunobiology. 2020;225(5):152009.
79. Yano S, Ashida K, Sakamoto R, et al. Human leucocyte antigen DR15, a possible predictive marker for immune checkpoint inhibitor-induced secondary adrenal insufficiency. Eur J Cancer. 2020;130:198-203.
80. Lu J, Li L, Lan Y, et al. Immune checkpoint inhibitor-associated pituitary-adrenal dysfunction: A systematic review and meta-analysis. Cancer Med. 2019;8(18):7503-15.
81. Di Dalmazi G, Ippolito S, Lupi I, et al. Hypophysitis induced by immune checkpoint inhibitors: a 10-year assessment. Expert Rev Endocrinol Metab. 2019;14(6):381-98.
82. Triggianese P, Novelli L, Galdiero MR, et al. Immune checkpoint inhibitors-induced autoimmunity: The impact of gender. Autoimmun Rev. 2020;19(8):102590.

83. Faje A, Reynolds K, Zubiri L, et al. Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab-associated hypophysitis. Eur J Endocrinol. 2019;181(3):211-9.
84. Cooksley T, Girotra M, Ginex P, et al. Multinational Association of Supportive Care in Cancer (MASCC) 2020 clinical practice recommendations for the management of immune checkpoint inhibitor endocrinopathies and the role of advanced practice providers in the management of immune-mediated toxicities. Support Care Cancer. 2020;28(12):6175-81.
85. De Sousa SMC, Sheriff N, Tran CH, et al. Fall in thyroid stimulating hormone (TSH) may be an early marker of ipilimumab-induced hypophysitis. Pituitary. 2018;21(3):274-82.
86. Siddiqui MS, Lai ZM, Spain L, et al. Predicting development of ipilimumab-induced hypophysitis: utility of T4 and TSH index but not TSH. J Endocrinol Invest. 2021;44(1):195-203.
87. Levy M, Abeillon J, Dalle S, et al. Anti-PD1 and Anti-PDL1-Induced Hypophysitis: A Cohort Study of 17 Patients with Longitudinal Follow-Up. J Clin Med. 2020;9(10).
88. Kurokawa R, Ota Y, Gonoi W, et al. MRI Findings of Immune Checkpoint Inhibitor-Induced Hypophysitis: Possible Association with Fibrosis. AJNR Am J Neuroradiol. 2020;41(9):1683-9.
89. Erra A, Pannu BS, Patel S, et al. A Rare Case of Ipilimumab-induced Reversible Hypophysitis and Permanent Primary Hypothyroidism. Cureus. 2019;11(6):e5001.