Diagnosis and treatment of autoimmune and IgG4-related hypophysitis: clinical guidelines of the Japan Endocrine Society

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Abstract. Hypophysitis, which is often accompanied by pituitary dysfunction, is classified into several subtypes based on the cause, histology, and the location of inflammation in the pituitary gland. A definitive diagnosis requires pituitary biopsy, which is invasive, and the process is limited to specialized clinical settings. In this opinion paper, we review the literature associated with hypophysitis, and provide the guidelines of the Japan Endocrine Society for the diagnosis and treatment of autoimmune and IgG4-related hypophysitis.

Key words: Pituitary, Autoimmunity, Hypopituitarism, Diabetes insipidus, IgG4

Autoimmune Hypophysitis

Overview

Hypophysitis is a chronic inflammatory disease in the pituitary gland that can lead to pituitary dysfunction [1]. Hypophysitis is classified as primary when the cause is unclear and the inflammation is confined to the pituitary, or secondary when the cause is clear and it is a manifestation of systemic diseases. Hypophysitis is also induced by drugs such as immune checkpoint inhibitors [2].

Primary hypophysitis is further classified into 4 subtypes based on histology: lymphocytic, granulomatous, xanthomatous, and necrotizing. Among these, lymphocytic hypophysitis is the most common [1]. Since a histopathological feature of lymphocytic hypophysitis is lymphocytic infiltration in the pituitary gland, autoimmunity has been implicated in its pathogenesis. This is why lymphocytic hypophysitis is also referred to as autoimmune hypophysitis [3].

According to the location of inflammation in the pituitary gland, primary hypophysitis is classified as follows: lymphocytic adenohypophysitis (LAH), lymphocytic infundibulo-neurohypophysitis (LINH), and lymphocytic panhypophysitis (LPH). It remains to be established whether these three subtypes are completely different diseases, or just different manifestations of the same disease.

Hypophysitis is a relatively rare condition, and previous studies suggest the incidence is 1 in 7–9 million/year [1, 4-6], although the diagnostic criteria vary among studies. The diagnosis of secondary hypophysitis is made if inflammatory lesions exist extra-pituitary, or a specific diagnostic marker of an inflammatory disease is present. On the other hand, primary hypophysitis is diagnosed only when other causative diseases are excluded [1]. There is no established serological marker to diagnose primary hypophysitis, and the definitive diagnosis of primary hypophysitis requires pituitary biopsy. Although the procedure is invasive, it should be considered when a precise diagnosis is required: e.g., malignant tumors are suspected, or the pituitary lesion grows progressively during follow-up. Pituitary biopsy is recommended before administration of pharmacological doses of glucocorticoids, and sampling from the appropriate pituitary lesion is essential for the correct diagnosis of hypophysitis.
Magnetic resonance imaging (MRI) is useful for evaluation and follow-up of lesions. Diffuse enlargement of the anterior pituitary, with homogenous and strong gadolinium enhancement in the lesion, is characteristic of LAH [7-9]. In LINH, the neurohypophysis or stalk is enlarged, and the lesion shows gadolinium enhancement [10, 11]. Both LAH and LINH findings are observed in LPH [12, 13].

In LAH, inflammation in the anterior pituitary gland causes a partial or complete deficit of anterior pituitary hormones, mainly ACTH, followed by TSH, gonadotropins, and PRL [1]. LAH is more common in women than in men, and often develops during pregnancy and postpartum [1, 9]. In LINH, which affects males and females equally [1], inflammation occurs in the posterior pituitary and stalk, leading to central diabetes insipidus [14]. LINH is thought to be a common cause of what was previously considered to be idiopathic diabetes insipidus [10], and the presence of anti-rabphilin-3A antibodies in the serum of patients with LINH has been reported [11]. In LPH, which is slightly more common in women than in men, but is not associated with pregnancy [1], inflammation spreads throughout the pituitary and causes deficits of both anterior and posterior pituitary hormones.

If primary hypophysitis is accompanied by deficits of pituitary hormones, replacement therapy is necessary. In cases where pituitary enlargement causes compressive symptoms such as visual field disturbance and headache, a pharmacological dose of glucocorticoids could be administered. Surgery is considered when the symptoms are severe, progressive, or refractory to glucocorticoid therapy. It is unclear whether administration of high doses of glucocorticoids prevents the progression of pituitary dysfunction.

Differential diagnosis of primary hypophysitis is listed as follows:
1. Systemic diseases
   1) Sarcoidosis
   2) Granulomatosis with polyangiitis
   3) Langerhans cell histiocytosis
   4) Syphilis
   5) Tuberculosis
   6) Mycoses
   7) IgG4-related disease
2. Sella and parasellar diseases
   1) Germinoma
   2) Rathke’s cleft cyst
   3) Craniopharyngioma
   4) Pituitary adenoma
   5) Chronic inflammation in parasellar lesions such as paranasal or cavernous sinus

### Diagnosis of Lymphocytic Adenohypophysitis (LAH)

#### I. Main symptoms
1. Symptoms due to mass lesion in pituitary gland, such as headache, visual field disturbance, and lactorrhea.
2. Symptoms due to hypopituitarism, such as general fatigue or amenorrhea.

#### II. Laboratory data and pathology
1. Decreased levels of one or more anterior pituitary hormones, as well as those from the targeted organs.
2. Impaired responses of anterior pituitary hormones in stimulation tests.
3. Diffuse enlargement of anterior pituitary gland.
4. Homogenous and strong enhancement of pituitary lesion on MRI with gadolinium-enhancement (Note 1).
5. Cell infiltration mainly consisting of lymphocytes in anterior pituitary gland in biopsy (Note 2).

#### III. Additional findings
1. LAH is more common in women, especially during pregnancy and postpartum.
2. Some patients with LAH show hyperprolactinemia.
3. LAH is often accompanied by other autoimmune diseases (e.g. chronic thyroiditis).
4. Anti-pituitary antibodies can be detected in some patients with LAH.
5. LAH can result in empty sella after a long-term follow-up.

#### Diagnostic Criteria

- Definitive diagnosis of LAH is made when the following is fulfilled: any of the items in I and all of the items in II.
- Probable diagnosis of LAH is established when the following is fulfilled: any of the items in I and items 1, 2, 3, and 4 in II.

#### Notes

1. Although rare, cystic changes in pituitary have been observed.
2. If pituitary biopsy reveals granulomatous, xanthomatous, or necrotizing lesions, it is diagnosed as granulomatous, xanthomatous, or necrotizing hypophysitis, respectively.
Diagnosis of Lymphocytic Infundibuloneurohypophysitis (LINH)

I. Main symptoms
Thirst, polydipsia and polyuria

II. Laboratory data and pathology
1. Laboratory findings that match the criteria of central diabetes insipidus.
2. Enlargement of the pituitary gland or a stalk on imaging.
3. Strong and diffuse enhancement in the neurohypophysis and/or stalk lesion on MRI with gadolinium-enhancement.
4. Cell infiltration mainly consisting of lymphocytes in the lesion in biopsy.

III. Additional information
1. In most cases, anterior pituitary function is preserved.
2. Enlargement of the pituitary gland or stalk often disappears in the natural course.

Diagnostic Criteria
– Definitive diagnosis of LINH is made when the following is fulfilled: all the items in I and all the items in II.
– Probable diagnosis of LINH is established when the following is fulfilled: all the items in I and items 1, 2, 3 in II.

Diagnosis of Lymphocytic Panhypophysitis (LPH)

I. Main symptoms
1. Symptoms due to mass lesion in pituitary gland, or those due to hypopituitarism.
2. Symptoms due to central diabetes insipidus.

II. Laboratory data and pathology
1. Decreased levels of one or more anterior pituitary hormones as well as those from the targeted organs.
2. Decreased responses of anterior pituitary hormones in stimulation tests.
3. Laboratory findings that match central diabetes insipidus (Note 1).
4. Diffuse enlargement of pituitary gland and/or stalk on imaging.
5. Homogenous and strong enhancement of pituitary gland or stalk lesion on MRI with gadolinium-enhancement.
6. Cell infiltration mainly consisting of lymphocytes in pituitary gland or stalk in biopsy (Note 2).

III. Additional findings
1. Some patients show hyperprolactinemia.
2. Dysfunction of both hypothalamus and pituitary is observed in some cases.

Diagnostic Criteria
– Definitive diagnosis of LPH is made when the following is fulfilled: all the items in I and all the items in II.
– Probable diagnosis of LPH is made when the following is fulfilled: all the items in I and items 1, 2, 3, 4, and 5 in II.

Notes
1. Symptoms of central diabetes insipidus may be masked if a patient has secondary adrenal insufficiency (masked diabetes insipidus).
2. If pituitary biopsy reveals granulomatous, xanthomatous, or necrotizing lesions, it is diagnosed as granulomatous, xanthomatous, or necrotizing hypophysitis, respectively.

Treatment of Autoimmune Hypophysitis
1. A pharmacological dose of glucocorticoids (e.g., 0.5 to 1.0 mg/kg/day of prednisolone) is administered if the pituitary enlargement is accompanied by compressive symptoms such as visual defects, visual acuity impairment or severe headache. Doses of glucocorticoids should be adjusted depending on ages of patients and the severity of the disease. The dosage of glucocorticoids is tapered if the symptoms improve. High-dose glucocorticoid therapy (pulse or mini-pulse therapy) is considered in severe cases. Pituitary biopsy and decompression by partial resection of the enlarged lesion is applicable if compressive symptoms are severe or progressive despite glucocorticoid therapy.
2. Differential diagnosis, consideration of the necessity of pituitary biopsy, and exclusion of infectious diseases, including tuberculosis, are required before administration of pharmacological doses of glucocorticoids.
3. Follow-up with the assessment of pituitary MRI, instead of administration of high doses of glucocorticoids, is recommended if the patient has no or mild symptoms associated with hypophysitis.
4. Adequate hormone replacement therapy based on the assessment of pituitary functions is required.
IgG4-related Hypophysitis

Overview

IgG4-related disease is a systemic disease characterized by infiltration with IgG4-positive plasma cells in various organs, including pancreas, bile duct, salivary glands, retroperitoneum, kidney, lung, meninges, aorta, thyroid and pituitary gland [15]. It has been proposed that IgG4-related hypophysitis is a part of a syndrome of IgG4-related disease [16, 17]. Although the prevalence of IgG4-related hypophysitis remains unknown, a study of 170 consecutive outpatients with hypopituitarism and/or central diabetes insipidus reported that IgG4-related hypophysitis was detected in 30% (7 of 23) of hypophysitis cases and 4% of all cases (7 of 170), suggesting that IgG4-related hypophysitis is not so rare [18]. Although the roles of IgG4 in hypophysitis remain unknown, autoantigen candidates (growth hormone and proopiomelanocortin) [19] and the presence of antipituitary antibodies [20] have been reported in patients with biopsy-proven IgG4-related hypophysitis, suggesting that autoimmunity is involved, at least in part, in the pathogenesis of IgG4-related disease [15]. Anterior pituitary dysfunction and/or central diabetes insipidus accompanied by enlargement of the pituitary gland and/or thickened stalk are often observed in patients with IgG4-related hypophysitis [16].

The diagnosis of IgG4-related disease relies on the histopathological findings. The international histological consensus criteria indicate that the IgG4/IgG-positive cell ratio must be greater than 40% for histological diagnosis of IgG4-related disease [21]. Diagnostic criteria provided by a Japanese research group convened to study IgG4-related disease organized by the Ministry of Health, Labor and Welfare Japan are as follows: (1) organ enlargement, mass or nodular lesion, or organ dysfunction; (2) a serum IgG4 concentration greater than 135 mg/dL, and (3) histopathological findings of greater than 10 IgG4-positive cells/high-powered field (HPF) of biopsy sample and a ratio of IgG4/IgG-positive cells greater than 40% [22]. Because an increased serum IgG4 level is not specific to this disease [15], differential diagnosis to exclude an infection, malignancy, inflammatory disease, and allergic disease is important. In addition, the presence of IgG4-positive plasma cells in the involved tissue is not specific to this disease; for example, IgG4-positive plasma cells have also been reported in Rathke’s cleft cyst and granulomatosis with polyangiitis [23, 24].

Definitive diagnosis of IgG4-related hypophysitis therefore requires pituitary biopsy, although the procedure is invasive and its application is limited to specialized clinical settings. If pituitary histopathology is not available, the presence of IgG4-positive cells in other organs suggests a probable diagnosis of IgG4-related hypophysitis. As for the cases where histopathology is not available, Leporati et al. proposed diagnostic criteria for IgG4-related hypophysitis, in which pituitary images, serum IgG4 levels, and responses to administration of glucocorticoids are involved [17].

Glucocorticoids often improve enlargement of pituitary gland and thickened stalk, although the most appropriate dose of glucocorticoids for treatment remains unclear. The symptoms associated with enlargement of pituitary, such as headache, visual field disturbance and lactorrhea, can be improved by glucocorticoids, while improvement of pituitary function is rare [16, 17]. Glucocorticoids can be terminated if patients are in remission for a long period of time, although discontinuation of glucocorticoids frequently causes a disease relapse not only in the pituitary but also in other organs.

Diagnosis of IgG4-related Hypophysitis

I. Main symptoms

1. Symptoms due to mass lesion in pituitary gland, or those due to hypopituitarism.
2. Symptoms due to central diabetes insipidus.

II. Laboratory data and pathology

1. Decreased levels of one or more anterior pituitary hormones and those from the targeted organs.
2. Decreased responses of anterior pituitary hormones in stimulation tests.
3. Laboratory data that match the criteria of central diabetes insipidus (Note 1).
4. Diffuse enlargement of pituitary gland and/or stalk on imaging.
5. Elevated levels of serum IgG4 (Note 2, 3).
6. Infiltration with IgG4-positive plasma cells in pituitary biopsy samples (Note 4, 5).
7. Infiltration with IgG4-positive plasma cells in other involved organs (Note 6).

III. Additional findings

1. IgG4-related hypophysitis is more common in elderly men.
2. Pituitary mass and thickened stalk often respond to glucocorticoid therapy. Flares of pituitary lesion during steroid tapering or development of new lesions in other organs should be monitored during a follow-up (Note 6).

Diagnostic Criteria

– Definitive diagnosis of IgG4-related hypophysitis is established when the following is fulfilled: any of
the items in I and items 1, 2, 4, and 6 in II, or any of the items in I and items 3, 4, and 6 in II.
– Probable diagnosis of IgG4-related hypophysitis is established when the following is fulfilled: any of the items in I and items 1, 2, 4, and 7 in II, or any of the items in I and items 3, 4, and 7 in II.
– Possible diagnosis of IgG4-related hypophysitis is established when the following is fulfilled: any of the items in I and items 1, 2, 4, and 5 in II, or any of the items in I and items 3, 4, and 5 in II.

Notes
1. Symptoms of central diabetes insipidus may be masked if a patient has secondary adrenal insufficiency (masked diabetes insipidus).
2. Serum IgG4 levels are more than 135 mg/dL. It is recommended that the levels are measured before the administration of glucocorticoids, which could decrease IgG4 levels. Serum levels of IgE can be increased in some patients with IgG4-related hypophysitis.
3. The number of IgG4-positive plasma cells is greater than 10 per high-power field or the ratio of IgG4/IgG-positive cells is more than 40%.
4. Retroperitoneal fibrosis, interstitial pneumonia, autoimmune pancreatitis, dacryoadenitis, and sialadenitis are often detected in IgG4-related disease.

Additional Statement
IgG4-related hypophysitis requires careful differential diagnosis from other pituitary diseases including pituitary adenoma, Rathke’s cleft cyst, craniopharyngioma, malignant lymphoma, and granulomatosis with polyangiitis which sometimes accompanies secondary infiltration with small numbers of IgG4-positive plasma cells.

Treatment of IgG4-related Hypophysitis
1. Recommendations for the treatment of IgG4-related disease should be followed [25, 26].
2. Glucocorticoids are the first-line agents for symptoms associated with pituitary enlargement. Doses of 30–40 mg/day of prednisolone are recommended as an initial dose.
3. Treatment with low doses of prednisolone should be continued even after pituitary enlargement is improved with high doses of prednisolone.
4. Treatment with prednisolone can be terminated if pituitary enlargement is improved for an extended period of time, although discontinuation of treatment frequently causes disease relapse.

Author Contributions
All authors discussed these diagnostic criteria. HA, SI and HT wrote the manuscript. All authors assisted with revision of the manuscript.

Disclosure Summary
The authors have nothing to disclose.

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