Review on Recent Topics in Hypophysitis

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The number of cases of lymphocytic hypophysitis is small, although the condition is not rare. For optimal therapy, the correct diagnosis from imaging, immunological studies, and pathological findings from a pituitary biopsy is important. Recently, anti-Rabphilin antibody has been proposed to be a biomarker for lymphocytic infundibulo-neurohypophysitis. Immunological disorders such as anti-Pit-1 antibody syndrome are similar to the pathogenesis of lymphocytic hypophysitis. Moreover, recent immune checkpoint blockade such as ipilimumab has been shown to induce anti-CTLA-4-related hypophysitis. In the future, elucidating the immunological mechanism and establishing a suitable therapy will be necessary for accurate long-term prognosis. (J Nippon Med Sch 2017; 84: 201–208)

Key words: hypophysitis, Rabphilin, Pit-1, immune checkpoint blockade

Introduction
The causes of hypopituitarism are various and have been extensively classified as tumor, inflammation, vascular accident, trauma, and congenital defects. In this article, pituitary inflammation, especially primary hypophysitis, is reviewed, including recent topics and our experience with cases. The etiology of primary hypophysitis is thought to be an autoimmune process, which pathogenesis is gradually turned out and new autoimmune process has been reported. Although pituitary biopsy is the gold standard for correct diagnosis, the procedure is invasive and not acceptable to all patients.

Definition and Classification
Hypophysitis is classified into primary and secondary forms. Primary forms are characterized by inflammation confined to the pituitary due to unknown etiology, and are classified by histopathological findings or the involved structures. Secondary forms are due to pituitary inflammatory processes triggered by definite etiology or pituitary involvement concomitant with more generalized known systemic diseases. Caturegli et al. reviewed the disease, showed that lymphocytic hypophysitis is classified into three forms, lymphocytic adenohypophysitis (LAH), lymphocytic infundibulo-neurohypophysitis (LINH), and lymphocytic panhypophysitis (LPH), and reported the number of each type of case during 1962–2004. They identified a total of 379 patients with primary hypophysitis, comprising 245 cases of LAH, 39 cases of LINH, and 95 cases of LPH. Adenohypophysitis mainly affects the anterior pituitary, and infundibulo-neurohypophysitis involves the posterior pituitary and stalk. However, panhypophysitis may be heterogeneous, and the pathogenesis includes local inflammation from the anterior pituitary, posterior pituitary, or pathological conditions of hypothalamic-pituitary region such as Rathke’s cyst, craniopharyngioma, or germinoma.

Clinical Presentation
Hypophysitis-related symptoms are headache, disturbances in visual acuity and the visual field, and hypopituitarism due to inflammation and compression of surrounding tissues by the enlarged pituitary. These symptoms are similar to those of pituitary adenomas. In non-functioning pituitary adenoma, growth hormone (GH) secretion is considered to be impaired early and first. In contrast, adrenocorticotropic hormone (ACTH) secretion is impaired first in most cases of hypophysitis. Increased prolactin (PRL) levels are observed in both conditions, resulting in decreased luteinizing hormone/follicle stimulating hormone. In hypophysitis, hypogonadism also occurs by damage of gonadotrophs due to inflammation.
LAH
LAH is the most common among the various types of hypophysitis and has been reported frequently during pregnancy and in the post-partum period. These characteristics are different from the other types of hypophysitis such as LINH, LPH, and IgG4-related hypophysitis in terms of the age and gender of patients. Several autoimmune diseases are associated with particular human leukocyte antigen (HLA) alleles. In patients with lymphocytic hypophysitis, HLA-DQ8 and HLA-DR53 are often expressed. The odds ratio of HLA-DQ8 in patients with lymphocytic hypophysitis was 23.1-fold higher than in controls with another sellar mass. An autoimmune etiology for LAH was suggested by the presence of anti-pituitary antibodies (APA), which recognize a 49-kDa protein corresponding to α-enolase or a 22-kDa protein corresponding to GH using the immunoblotting method. Pituitary gland-specific factor 1a was also suggested as an autoantigen of APA; however, these antibodies are not specific to hypophysitis. Hypophysitis-induced hypopituitarism shows various combinations of pituitary hormone deficiency. One mechanism is the presence of antibodies to both the hypothalamus and pituitary. The occurrence of central diabetes insipidus (CDI) in patients with lymphocytic hypophysitis seems to be due to autoimmune hypothalamic involvement rather than an expansion of the pituitary inflammatory process. A search for arginine vasopressin (AVP) antibodies with the immunofluorescence method in these patients may help to identify patients who are prone to developing autoimmune CDI. The detection of anti-hypothalamic antibody targeting corticotropin-releasing hormone (CRH) -secreting cells in some patients with GH/ACTH deficiency but with APA targeting only GH-secreting cells indicates that an autoimmune aggression to the hypothalamus is jointly responsible for their LAH. Consequently, not only pituitary but also hypothalamic autoimmunity may contribute to anterior pituitary dysfunction in LAH.

LINH
LINH is an uncommon inflammatory disorder that is often reported in men. LINH selectively affects the posterior pituitary and the pituitary stalk, resulting in CDI, and is frequently accompanied by hyperprolactinemia. Magnetic resonance imaging (MRI) findings are loss of the posterior pituitary bright spot and thickening of the infundibular stalk. CDI is associated with other autoimmune endocrine conditions along with detection of autoantibodies to AVP-secreting cells (AVPcAb) in a few cases. AVPcAb alone is not a good diagnostic marker for LINH but serves as guide and predictive marker of gestational or post-partum autoimmune CDI. Iwama et al. reported that Rabphilin (Rab) antibody is detected in patients with LINH. Rab is involved in the release of hormones or neurotransmitters and is expressed mainly in the brain, including the posterior pituitary and hypothalamus where AVP is present. Whether Rab antibodies are a cause of CDI or a result of LINH is unknown. However, Rab antibodies are detected in 76% of patients with LINH and 11% of patients with LAH. In contrast, these antibodies are absent in patients with sellar/suprasellar masses without lymphocytic hypophysitis, suggesting that this antibody may serve as a biomarker for the diagnosis of LINH and may be useful for the differential diagnosis in patients with CDI.

We experienced a case of LINH. A 26-year-old female with polydipsia and polyuria was diagnosed with CDI. MRI showed pituitary stalk thickening, suggesting the

<table>
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<th>Primary</th>
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<tr>
<td>Lymphocytic hypophysitis</td>
<td>Systemic disease</td>
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<tr>
<td>Lymphocytic adenohypophysitis</td>
<td>Takayasu’s disease</td>
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<td>Lymphocytic infundibulo-neurohypophysitis</td>
<td>Langerhans cell histiocytosis</td>
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<td>Lymphocytic panhypophysitis</td>
<td>Crohn’s disease</td>
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<td>Granulomatous hypophysitis</td>
<td>Sarcoidosis</td>
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<td>Xanthomatous hypophysitis</td>
<td>Inflammatory pseudotumor</td>
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<td>Necrotizing hypophysitis</td>
<td>Infective etiology</td>
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<td>IgG4-related hypophysitis</td>
<td>Bacterial, viral, fungal disease</td>
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<td>Mixed forms</td>
<td>Drug</td>
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<td></td>
<td>CTLA-4 blocking antibodies</td>
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<td>Interferon</td>
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Table 1 Classification of hypophysitis

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Fig. 1  A, C: Gadolinium-enhanced MRI brain scan demonstrated the enlarged posterior lobe and pituitary stalk. B, D: After 2 months, the posterior lobe and stalk enlargements were slightly decreased. A and B show sagittal sections. C and D show coronal sections.

possibility of LINH (Fig. 1). However, a parasellar tumor such as a germinoma could not be excluded, but a pituitary biopsy was declined by the patient. Two months later, MRI showed a slight decrease in the size of the pituitary stalk and pituitary (Fig. 1), suggesting a low possibility of malignancy including germinoma. Circulating anti-Rab antibody was demonstrated in her serum (unpublished data).

IgG4-related Hypophysitis

IgG4-related hypophysitis is thought to be a variant of LAH and a secondary form of LINH with IgG4-related systemic disease. This disease occurs in middle-aged and elderly men, and the etiology is unknown. Pituitary enlargement, infiltration of IgG4 plasma cells, and fibrosis in the affected pituitary are characteristic features, along with elevated serum IgG4 levels. This disease involves various tissues and is associated with Mikulicz’s disease, autoimmune pancreatitis, Riedel’s thyroiditis, and retroperitoneal fibrosis. Swelling of other organs is observed coincidentally or in disorder. Shimatsu et al. analyzed 22 cases and described eight clinical characteristics of pituitary and stalk lesions associated with IgG4-related systemic disease. Thereafter, Leporati et al. proposed five criteria to establish a diagnosis of IgG4-related hypophysitis (Table 2). Almost all cases of IgG4-related hypophysitis show hypopituitarism and/or CDI, although a case of IgG4-related hypophysitis without pituitary insufficiency was reported. Bando et al. observed 23 hypophysitis cases among 170 cases of hypopituitarism, of which seven cases (4%) were IgG4-related hypophysitis, suggesting that IgG4-related hypophysitis may not be rare.

We experienced a case with CDI, amenorrhea, and right abducens nerve palsy, which was diagnosed as IgG4-related hypophysitis following a pituitary biopsy. MRI findings showed hypophysitis spreading suprasellar and over the right cavernous sinus (Fig. 2). Pituitary enlargement and cavernous infiltration decreased after glucocorticoid therapy (Fig. 2). The right abducens nerve palsy disappeared, and menstruation resumed, however, CDI persisted (unpublished data). IgG4-related disease was first proposed as a cause of autoimmune pancreatitis in Japan. Thereafter, most cases of IgG4-related hypophysitis have been reported in Japan. Although the precise reason is unknown, racial differences, increased
Table 2  Diagnostic criteria for IgG4-related hypophysitis

<table>
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<tr>
<th>Criterion</th>
<th>Description</th>
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<tr>
<td>1</td>
<td>Pituitary histopathology</td>
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<td>Mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with more than 10 IgG4-positive cells per high-power field</td>
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<td>2</td>
<td>Pituitary MRI</td>
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<td>Sellar mass and/or thickened pituitary stalk</td>
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<td>3</td>
<td>Biopsy-proven involvement in other organs</td>
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<td></td>
<td>Association with IgG4-positive lesions in other organs</td>
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<td>4</td>
<td>Serology</td>
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<td></td>
<td>Increased serum IgG4 (&gt;140 mg/dL)</td>
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<td>5</td>
<td>Response to glucocorticoids</td>
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<td>Shrinkage of the pituitary mass and symptom improvement with steroids</td>
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Diagnosis of IgG4-related hypophysitis is established

- Criterion 1
- Criterion 2 and 3
- Criterion 2, 4, and 5

Fig. 2  A, C: Gadolinium-enhanced MRI brain scan demonstrated the enlarged pituitary and right cavernous infiltration. B, D: After 2 months of glucocorticoid therapy, the pituitary and cavernous infiltration were markedly decreased. A and B show coronal sections. C and D show sagittal sections.

Awareness of IgG4-related disease, and easy accessibility to MRI in Japan may be the reasons.

Anti-Pit-1 Antibody Syndrome

Congenital combined TSH, GH, and PRL deficiency due to a Pit-1 gene mutation is a well-known cause of short stature and failure to develop. Pit-1 is essential for the
drome (unpublished data).

cancer was not known. This case may be associated with multiple metastatic liver tumors for which the primary TSH deficiency. Circulating antibodies that reacted with syndromes. An 85-year-old man with general malaise and anti-Pit-1 antibody syndrome to toxic T cells that react against Pit-1 may be the cause of Pit-1 antibody in their serum was demonstrated. Cytotoxic lymphocytes aged 44, 75, and 78 years old. Circulating anti-GH deficiency is assessed rarely. CDI was reported in only one thymomas, lactotrophs, and thyrotrophs in the pituitary. Yamamoto et al. described three cases of acquired combined TSH, GH, and PRL deficiency. The patients were all males aged 44, 75, and 78 years old. Circulating anti-Pit-1 antibody in their serum was demonstrated. Cyto-toxic T cells that react against Pit-1 may be the cause of ymoma plays a causal role in the development of this syndrome.

We experienced a fourth case of anti-Pit-1 antibody syndrome. An 85-year-old man with general malaise and peripheral edema was diagnosed with GH, PRL, and TSH deficiency. Circulating antibodies that reacted with Pit-1 were observed. However, he had no thymoma but multiple metastatic liver tumors for which the primary cancer was not known. This case may be associated with immune-related cytotoxicity due to paraneoplastic syndrome (unpublished data).

**Immune Checkpoint Blockade-related Hypophysitis**

Immune checkpoint blockade such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies or programmed cell death protein 1 (PD-1) antibodies is now used for cancer therapy. Sometimes, immune-related adverse events (IRAEs) are recognized and one of the endocrine IRAEs is hypophysitis. Hypophysitis occurs at a frequency of 9.1% and generally at 6–12 weeks after treatment in older males. Secondary adrenal failure, hypothyroid, and hypogonadism are common but GH deficiency is assessed rarely. CDI was reported in only one case. PRL increases or decreases, and recovery of ACTH is less frequent. Cases with antibodies to pituitary cells were identified as LAH. The hypothesized mechanism is that IgG1, which activates the classic complement pathway, may be a mechanism of anti-CTLA-4-related hypophysitis, because CTLA-4 antibodies belong to the IgG1 class. Because pituitary swelling is followed by shrinkage, normal MRI does not rule out hypophysitis. Unlike ipilimumab, nivolumab, a PD-1 antibody, has not been linked to an increased incidence of hypophysitis, which occurs in <1% of patients. The reason for the discrepancy in the occurrence rate between CTLA-4 antibodies and PD-1 antibodies is that pituitary cells express ectopic CTLA-4, resulting in CTLA-4 antibody-induced hypophysitis.

**Imaging Study**

MRI findings in the case of hypophysitis indicate pituitary enlargement with symmetrical expansion and intense and homogeneous enhancement of the pituitary mass with gadolinium. Dural tail sign is positive, a condition seen on contrast-enhanced MRI as a thickening of the enhanced dura matter that resembles a tail extending from a mass, although this sign is not specific to hypophysitis. The pituitary stalk is thickened but not deviated. On the contrary, a unilateral endosellar mass, a nonhomogeneously expanding pituitary mass with asymmetrical extension, or delayed and nonhomogeneous enhancement suggests a pituitary adenoma. The pituitary stalk is deviated contralaterally in a pituitary adenoma (Table 3).

We observed a case that was diagnosed as a pituitary adenoma from MRI findings, which showed a less enhanced lesion by gadolinium (Fig. 3). However, the pathological diagnosis was xanthomatous hypophysitis (unpublished data). Therefore, differentiating pituitary differentiation, proliferation, and maintenance of somatotrophs, lactotrophs, and thyrotrophs in the pituitary.

Table 3  Differential imaging characteristics of the hypothalamic-pituitary region in lymphocytic hypophysitis and pituitary adenoma (revised from reference 2)

<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>Lymphocytic hypophysitis</th>
<th>Pituitary adenoma</th>
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<tbody>
<tr>
<td>MRI</td>
<td>Pituitary enlargement with symmetrical suprasellar expansion. Compression and displacement of chiasma. Stalk thickened but not deviated.</td>
<td>Unilateral endosellar mass (microadenoma) or inhomogeneously expanding pituitary mass with asymmetrical suprasellar extension (macroadenoma). Contralateral deviation of stalk.</td>
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adenoma from other pituitary mass lesions with only MRI may be impossible.

Although to a large degree, one can differentiate adenohypophysitis from pituitary adenoma, IFNH is difficult to discriminate from a tumor such as germinoma with MRI. Tumor markers such as alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG)-β, or placental alkaline phosphatase (ALP) in the cerebrospinal fluid are useful for diagnosing germinoma. However, a pituitary biopsy is the gold standard for differentiating IFNH from a germinoma. As mentioned above, excluding a germinoma by assaying for Rab antibodies may be helpful.

Therapy

Because hypophysitis is self-limiting, and spontaneous remissions can occur, therapy is not always necessary. Patients with extrasellar expansion of an enlarged pituitary and hypopituitary are treated with therapies. Conservative management is recommended for lymphocytic hypophysitis unless symptoms are severe or progressive.

Surgical indications: Surgery should be performed only in cases with serious and progressive deficits of the visual field, visual acuity, or ocular movements due to compression or infiltration, and that are not responsive to medical treatment.

Medical therapy: Glucocorticoids almost always improve the swelling of the pituitary and pituitary stalk, often with recovery of anterior pituitary function. CDI rarely improves with glucocorticoids. One report described a case of LINH in which CDI ceased after glucocorticoid therapy. The most commonly used glucocorticoids are prednisone, hydrocortisone, and methylprednisolone. Considering the absence of control studies, concluding that glucocorticoids are preferable is difficult. Some anterior pituitary insufficiencies are resolved by glucocorticoids, even in a lower dose range. In glucocorticoid-resistant cases, immunosuppressive drugs such as azathioprine, methotrexate, and cyclosporine A have been used successfully. However, the long-term effects are unclear. Recently, rituximab, a monoclonal anti-
body that lyse B cells expressing CD20, has been employed to treat steroid-refractory lymphocytic hypophysitis and IgG4-related disease, suggesting that rituximab could be considered a new option for the treatment of some types of LAH.

Hormone replacement: Glucocorticoid deficiency should be used first to avoid a potential adrenal crisis that may be precipitated by replacing thyroid hormone first. Because adrenal insufficiency may mask the presence of partial CDI, monitoring patients for the development of diabetes insipidus after starting glucocorticoid replacement has been suggested. Hormone replacement should be consistent with the current Endocrine Society Clinical Practice Guidelines.

Treatment in the Future

No consensus treatment for lymphocytic hypophysitis has been established, and long-term outcomes are not known. Therefore, a prospective randomized study is desirable to further elucidate the treatment, and long-term follow-up of the outcome in multiple institutes is necessary due to the low incidence of lymphocytic hypophysitis. Then, selection of an appropriate, personalized therapy for each type of hypophysitis and severity of symptoms may be possible.

Conflict of Interest: The author declares no conflict of interest.

References


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