Anti-pituitary antibodies as a marker of autoimmunity in pituitary glands

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Abstract. Autoimmunity contributes to the pathogenesis of hypophysitis, a chronic inflammatory disease in the pituitary gland. Although primary hypophysitis is rare, the number of pituitary dysfunction cases induced by immune checkpoint inhibitors (ICIs) is increasing. While it is difficult to prove the involvement of autoimmunity in the pituitary glands, circulating anti-pituitary antibodies (APAs) can be measured by indirect immunofluorescence and used as a surrogate marker of pituitary autoimmunity. APAs are present in several pituitary diseases, including lymphocytic adenohypophysitis, lymphocytic infundibulo-neurohypophysitis (LINH), IgG4-related hypophysitis, and pituitary dysfunction induced by ICIs. Mass spectrometry analysis of antigens targeted by APAs clarified rabphilin-3A as an autoantigen in LINH. This demonstrates that APAs can be applied as a probe to identify novel autoantigens in other pituitary autoimmune diseases, including pituitary dysfunction induced by ICIs, which can aid in biomarker discovery.

Key words: Hypopituitarism, Diabetes insipidus, Programmed cell death 1, Cytotoxic T-lymphocyte associated protein 4, Autoantibody

Anti-pituitary Antibodies (APAs)

Until there are validated autoantigens for primary hypophysitis, autoantibodies and T cell responses to specific pituitary gland antigens cannot be quantified. However, evaluating the presence of circulating autoantibodies against pituitary glands (APAs) can provide an estimate of pituitary autoimmunity. In this approach, indirect immunofluorescence (IIF), using patients’ sera as primary antibodies and pituitary glands from healthy subjects as substrates, measures the presence of APAs. The identification of APAs by IIF was first reported in patients with autoimmune diseases, including Hashimoto’s thyroiditis [12]. Previous studies have detected APAs using pituitary glands from a variety of species, including

lymphocytic panhypophysitis [3].

The definitive diagnosis of primary hypophysitis requires pituitary biopsy. However, pituitary biopsies are invasive and not always performed in clinical practice. There are currently no specific biomarkers to diagnose primary hypophysitis, although several studies have reported candidate autoantigens, including α-enolase [6, 7], growth hormone (GH) [8], pituitary gland specific factor (PGSF) 1a [9], PGSF2 [9], secretogranin II [10], chromosome 14 open reading frame 166 (C14orf166) [11], and chorionic somatomammotropin [11].

Autoimmune Hypophysitis

Hypophysitis, a chronic inflammatory disease of the pituitary gland, can cause hypopituitarism and central diabetes insipidus and is classified based on etiology as primary or secondary forms [1-3]. While the cause of primary hypophysitis is unclear, secondary hypophysitis can arise from several systemic, sellar, and parasellar diseases, including tumors, which are accompanied by inflammation in the pituitary glands [1-3]. Drugs such as immune checkpoint inhibitors (ICIs) can also induce secondary hypophysitis [4].

Four subtypes of primary hypophysitis, based on histological characteristics, are lymphocytic, granulomatous, xanthomatous, and necrotizing. Lymphocytic hypophysitis, also called autoimmune hypophysitis, is the most common and is characterized by infiltration of lymphocytes in the pituitary gland [1, 5]. Lymphocytic hypophysitis is further classified according to the site of inflammation as lymphocytic adenohypophysitis (LAH), lymphocytic infundibulo-neurohypophysitis (LINH), or lymphocytic panhypophysitis [3].
human, baboon, rhesus macaque, rat, mouse, cow, guinea pig, sheep, and pig [1]. Ricciuti A. et al. reported that detecting APAs using healthy human pituitary sections enabled greater sensitivity and specificity compared to cynomolgus monkey, dog, and mouse pituitary sections [13]. Using this assay, they found that the prevalence of APAs was significantly higher in patients with pituitary diseases compared to healthy controls [95 of 390 (24%) vs. 3 of 60 (5%), \( p = 0.001 \)] [13]. Among pituitary diseases, biopsy-proven hypophysitis showed the highest prevalence of APAs (14 of 31, 45.2%). However, APAs were also detected in other pituitary diseases, including germinoma [3 of 9 (33.3%)], isolated hormone deficiency [6 of 21 (28.6%)], and Rathke cleft cysts [3 of 12 (25.0%)]. In addition, the APA staining pattern was classified into four types [granular cytosolic, diffuse cytosolic, perinuclear, mixed (diffuse and perinuclear)] (refer to Figure 4 in [13]), among which a granular cytosolic pattern was most commonly found in patients with hypophysitis, suggesting that this pattern indicates the presence of pituitary autoimmunity [13]. Together, the presence of APAs is not specific for autoimmune hypophysitis but may be useful to speculate the presence of autoimmunity against pituitary antigens.

Interestingly, it has been reported that APAs are present in the sera of some patients with traumatic brain injury (TBI) [14]. TBI patients with APAs exhibited a significantly higher frequency of pituitary dysfunction compared to TBI patients without APAs (46.2% vs. 12.5%) [14]. APAs were also identified in some patients with an anterior pituitary hormone deficiency, including GH [15], prolactin [16], and ACTH [13]. These findings suggest that autoimmunity is involved in the development of TBI-induced hypopituitarism and isolated pituitary hormone deficiency.

### APAs in LAH

Patients with LAH show infiltration of lymphocytes in the anterior pituitary glands and a partial or complete deficit of anterior pituitary hormones, mainly adrenocorticotropic hormone (ACTH), followed by thyroid-stimulating hormone (TSH), gonadotropins, and prolactin [1]. In LAH, the autoimmune response, including autoantibodies and autoreactive T cells, is thought to be directed against anterior pituitary cells. A previous study used double IIF on a subset of hypophysitis patients with APAs to identify the targeted pituitary cells and found that APAs most frequently recognized FSH-secreting cells, followed by TSH-, LH-, and ACTH-secreting cells [13], suggesting that these cells express autoantigens. However, the specific autoantigens targeted in LAH remain unknown. Interestingly, ACTH deficiency is most frequently observed in patients with LAH [1], even though APAs recognize anterior pituitary cells secreting other hormones with higher frequency [13]. It is possible that APAs may develop secondary to pituitary inflammation and that the sensitivity of IIF is low and cannot detect low titers of APAs. However, the pathophysiological roles of APAs remain unclear.

Since the development of LAH is associated with pregnancy, LAH is more common in females, who likely present at a younger age than males [1]. It remains unknown if the prevalence of APAs in LAH varies with gender and age.

### APAs in LINH

Patients with LINH show inflammation in the posterior pituitary and/or pituitary stalk, leading to central diabetes insipidis [3]. LINH is thought to be a cause of idiopathic central diabetes insipidus (CDI) and has an autoimmune etiology [17]. It has been reported that patients with idiopathic CDI or LINH exhibit cytoplasmic autoantibodies targeting vasopressin-cells (AVPc-Abs) [18-20]. However, AVPc-Abs are also present in patients with other diseases, including Langerhans cell histiocytosis and germinoma [21]. These findings suggest that AVP neurons may express autoantigens. We tested for the presence of autoantibodies against the posterior pituitary gland in sera from patients with LINH and showed that some biopsy-proven LINH patients had autoantibodies against rat posterior pituitary glands [22]. Based on these findings, autoantigens were exhaustively examined by mass spectrometry analysis after immunoprecipitation of posterior pituitary lysate with each serum sample from 3 LINH patients (Fig. 1). Among the candidates, including vesicle-associated proteins, that overlapped between patients, rabphilin-3A was identified as a targeted autoantigen in LINH [22]. Anti-rabphilin-3A antibodies were detected in 22 of the 29 (76%) patients with LINH, including all of the 4 biopsy-proven samples, but not in patients with biopsy-proven sellar or suprasellar masses without lymphohypophysitis \((n = 34)\). However, anti-rabphilin-3A antibodies were also present in a subset of sera from patients with other autoimmune diseases \([10 of 70 (14\%)\), including rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroid diseases, as well as healthy subjects \([5 of 41 (12\%)\)] [22]. Anti-rabphilin-3A antibodies can be detected in patient serum by testing for recognition of full length recombinant human rabphilin-3A protein by Western blotting [22]. Although the specific epitope of rabphilin-3A targeted by anti-rabphilin-3A antibodies for patients with LINH remains unknown, anti-rabphilin-3A antibodies may be a candidate biomarker for the diagnosis of LINH.
However, there are currently no ELISAs available to measure anti-rabphilin-3A antibodies, and further studies are required to use anti-rabphilin-3A antibodies as a non-invasive biomarker for LINH diagnosis. Interestingly, Yasuda Y. et al. recently showed that immunization with rabphilin-3A protein caused lymphocytic infiltration in the posterior pituitary glands and increased urine volume in SJL mice [23], suggesting the involvement of rabphilin-3A as a pathogenic autoantigen in LINH.

In contrast to LAH, the development of LINH is not associated with pregnancy, and the incidence of LINH seems to be equal in males and females [1]. In addition, the mean age of LINH onset is higher compared to LAH [1]. However, whether APA positivity is associated with gender or age in patients with LINH is unknown.

**APAs in IgG4-related Hypophysitis (IgG4-RH)**

IgG4-related disease is a systemic disease characterized by infiltration of IgG4-positive plasma cells in various organs, including the pituitary gland [24]. IgG4-RH, a part of systemic IgG4-related diseases, is frequently observed in elderly males and can cause hypopituitarism and central diabetes insipidus [25, 26]. It has been reported that autoimmunity is involved, at least in part, in the pathogenesis of IgG4-related disease [24]. We detected APAs in sera from 5 of 17 patients (29%) with IgG4-RH by IIF on human pituitary substrates [27]. Double IIF revealed that the endocrine cells targeted by APAs in the 5 IgG4-RH cases were exclusively corticotrophs. Surprisingly, the IgG subclass of the APAs was IgG1, not IgG4, in all 5 cases, suggesting that IgG4 is not directly involved in the pathophysiology of IgG4-RH. We also found that APAs recognized proopiomelanocortin in 2 of the cases [27]. Another study also reported GH and proopiomelanocortin as candidate autoantigens in patients with biopsy-proven IgG4-RH [28]. These data suggest an immune response against the pituitary glands is involved in the pathogenesis of IgG4-RH. However, the role of IgG4 in hypophysitis remains unknown.

**Pituitary Dysfunction Induced by ICIs**

ICIs, including monoclonal antibodies against cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1), or programmed cell death-1 ligand 1 (PD-L1), have been widely used for several types of advanced malignancies. However, these drugs can cause immune-related adverse events (irAEs) in several tissues, including the skin [29], gastrointestinal tract [30], liver [31], lung [32], kidney [33], muscle [34], nerve [35], and endocrine glands [36]. Endocrine irAEs include hypopituitarism [37], primary adrenal insufficiency [38, 39], thyroid dysfunction [40], hypoparathyroidism [41-43], and type 1 diabetes mellitus [44], which can result in life-threatening consequences, such as adrenal crisis, thyroid storm, severe hypocalcemia, and diabetic ketoacidosis [4]. Recently, we demonstrated that pituitary dysfunction induced by ICIs (pituitary-irAEs) has two different disease types: hypophysitis with deficiency of multiple anterior pituitary hormones accompanied by pituitary enlargement (ICI-H), and isolated ACTH deficiency without pituitary enlargement (ICI-IAD). Interestingly, all of the patients with pituitary-irAEs exhibited ACTH deficiency [45]. Anti-CTLA-4 antibodies can cause both ICI-H and ICI-IAD, while anti-PD-1 antibodies only cause ICI-IAD [45]. Anti-PD-L1 antibodies can also cause ICI-IAD [46]. Recently, we discovered that the development of pituitary-irAEs was associated with prolonged overall survival in patients with non-small cell lung carcinoma or malignant melanoma treated with physiological doses of hydrocortisone [45]. Patients who developed pituitary-irAEs also showed hyponatremia with higher frequency compared to those who did not.
[6/16 (37.5%) vs. 10/120 (8.3%), p < 0.01] [45]. In addition to hyponatremia, some patients with pituitary-irAE induced by ICIs exhibited eosinophilia [47-49]. Therefore, to avoid overlooking ACTH deficiency during ICI treatment, pituitary hormones should be measured when pituitary-irAEs are suspected based on hyponatremia or eosinophilia. Also, appropriate management of pituitary-irAEs contribute to the prolonged overall survival in non-small cell lung carcinoma and malignant melanoma.

Biomarkers for Endocrine irAEs

Predictive biomarkers for ICIs are necessary to determine how a patient will respond to treatment, including their risk of developing irAEs [50]. We recently identified the presence of anti-thyroid antibodies (anti-thyroglobulin antibodies and/or anti-thyroid peroxidase antibodies) at baseline and irregular echo pattern in the thyroid gland as biomarkers to identify patients at high-risk of thyroid dysfunction following treatment with the anti-PD-1 antibodies, nivolumab and pembrolizumab [40, 51, 52]. Tahir SA et al, reported that serological analysis of recombinant cDNA expression libraries on brain tissue identified autoantibodies against guanine nucleotide-binding protein G(olf) subunit alpha (GNAL) and integral membrane protein 2B (ITM2B) as biomarkers for pituitary-irAEs [53]. However, this study only analyzed a small number of patients with pituitary dysfunction, including ICI-H and ICI-IAD. Future studies are required in a larger number of patients to validate the clinical utility of these antibodies. We also hypothesize that there are different autoantigens targeted in ICI-H and ICI-IAD. Based on our clinical findings that the development of pituitary-irAEs was associated with prolonged overall survival [45], biomarkers for pituitary-irAEs may predict ICI response.

Autoantibodies in ICI-H

We used IIF on healthy human pituitary substrates to examine APAs in the sera of patients with pituitary-irAEs induced by the anti-CTLA-4 antibody, ipilimumab. We identified APAs at the onset of pituitary-irAEs in all 7 patients tested [37]. In contrast, none of these patients exhibited APAs before the administration of ipilimumab. A patient who developed pituitary dysfunction following anti-PD-L1 treatment also tested positive for APAs [54]. However, the presence of APAs remains unknown in patients who developed ICI-IAD following anti-PD-1 treatment. There are also no reports identifying APAs at baseline in patients who develop pituitary-irAEs. Higher sensitivity assays are required to analyze APAs prior to onset as IIF may not detect low levels of APAs. Future studies to identify the autoantigens targeted by APAs in patients with pituitary-irAEs could help in the development of ELISAs that can predict the risk of pituitary-irAEs.

Animal model of ICI-H

The pathogenesis of irAEs is hypothesized to involve autoimmune reactions in a wide spectrum of tissues. However, it is unclear why the frequency of irAEs in each tissue varies among the different ICIs [36]. For example, we demonstrated that the frequencies of pituitary-irAEs were 24% and 6% during treatments with ipilimumab and anti-PD-1 antibodies, respectively [45]. To examine why ipilimumab caused a higher frequency of pituitary-irAEs, we established a mouse model of hypophysitis by repeated injections of an anti-CTLA-4 antibody of the IgG1 subclass. Following anti-CTLA-4 injection, mice developed pituitary inflammation and circulating APAs, suggesting the presence of pituitary autoimmunity [37]. In these mice, pituitary cells, specifically the thyrotropin- and prolactin-secreting cells, expressed CTLA-4. Interestingly, C4d was deposited on the pituitary cells, indicating complement activation following the binding of the anti-CTLA-4 antibody to pituitary cells [37] (Fig. 2). Together, this data suggests that the complement pathway contributes to pituitary autoimmunity, but future studies are required to clarify this mechanism.

Conclusion

Circulating APAs can be detected in several pituitary diseases and are useful as a surrogate marker of autoimmunity against pituitary glands. Rabphilin-3A was identified as an autoantigen in LINH through an exhaustive analysis of autoantigens by using APAs as a probe. Applying this strategy for other pituitary diseases, including pituitary-irAEs induced by ICIs, will help to identify novel autoantigens to aid in biomarker discovery.

Author Contributions

SI wrote the manuscript. SI and HA were involved in revising the manuscript.

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Fig. 2 Complement activation after anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibody injection in mice

Following the injection of an anti-CTLA-4 antibody of the IgG1 subclass into mice, the anti-CTLA-4 antibody directly binds to CTLA-4 expressed on a subset of pituitary cells, including thyroid-stimulating hormone (TSH) and prolactin (PRL) secreting cells, resulting in complement activation. Therefore, C4d deposition can be observed in the pituitary glands of these mice. We hypothesize that complement activation damages the pituitary cells and induces infiltration of inflammatory cells into the pituitary glands, ultimately resulting in the development of autoimmune hypophysitis and circulating anti-pituitary antibodies.

Disclosure Summary

The author has nothing to disclose.

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