MECHANISMS IN ENDOCRINOLOGY

Autoimmune hypopituitarism: novel mechanistic insights

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Abstract

Hypopituitarism is caused by various insults to the pituitary, such as hypothalamic and pituitary tumors, inflammation, autoimmunity, vascular injury, genetic abnormalities, irradiation, and trauma. Recently, it has been found that autoimmunity to the pituitary involves many pathological conditions associated with specific or non-specific hormone deficiencies in the gland. This review discusses the recent findings on the underlying mechanism of autoimmune hypopituitarism particularly of lymphocytic hypophysitis, IgG4-related hypophysitis, immune checkpoint inhibitor-induced hypophysitis, anti-PIT-1 hypophysitis, and isolated ACTH deficiency.

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Introduction

Hypopituitarism is defined as the deficiency of one or more pituitary hormones. Although a pituitary tumor is the most common cause, a tumor or cyst in the hypothalamus or infundibulum, infiltrative, vascular, and other disorders, and pituitary or cranial radiation therapy may also cause hypopituitarism (1). Recently, it has emerged that autoimmunity to the pituitary involves many pathological conditions associated with specific or non-specific hormone deficiencies.

Hypophysitis can occur as a primary entity or secondary to local or systemic disorders. Primary hypophysitis is further classified as lymphocytic hypophysitis, granulomatous hypophysitis, xanthomatous

hypophysitis, and necrotizing hypophysitis on the basis of histological features (2, 3). Lymphocytic hypophysitis (autoimmune hypophysitis) is an autoimmune pituitary disease and is caused by immune-mediated diffuse infiltration of lymphocytes and plasma cells. IgG4-related hypophysitis is a recently discovered subtype of autoimmune hypophysitis associated with multi-organ IgG4-related systemic disease (IgG4-RD). Pituitary involvement of IgG4-RD had initially been considered rare, but recent studies (4, 5) have suggested that its prevalence is underestimated. In these conditions, mostly non-specific anterior pituitary hormone deficiencies and/or central diabetes mellitus are observed.

Invited Author's profile

Yutaka Takahashi, MD, PhD, is Associate Professor of Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Japan. His research activities focus on pituitary diseases. He has researched and reported on the association between adult GH deficiency and NASH, a novel clinical entity 'anti-PIT-1 antibody syndrome'. More recently, he has reported the application of induced pluripotent stem cells on the pathophysiology of congenital pituitary hypoplasia.

Hypophysitis is also associated with several kinds of drugs. Although various forms of drug-induced hypophysitis have been reported, with the induction of immunotherapy for many kinds of cancers, immune check point inhibitor-induced (ICI-induced) hypophysitis has emerged as an immune-related adverse event (IrAE). Interestingly, relatively specific hormone deficiency has been detected in ICI-induced hypophysitis.

In other autoimmune pituitary diseases, specific anterior pituitary defects have been reported. For example, several conditions of isolated anterior pituitary hormone deficiencies including ACTH, LH/FSH, GH, and PRL have been reported, where specific autoantibodies against each type of anterior pituitary hormone have been detected (6), although isolated ACTH deficiency is found to be prevalent. Anti-PIT-1 hypophysitis (also called as anti-PIT-1 antibody syndrome) involves specific deficiency in GH, PRL, and TSH (7). As mentioned previously, ICI-induced hypophysitis shows a predominant deficiency in ACTH, LH/FSH, and TSH in CTLA-4 inhibitor-induced hypophysitis and in ACTH in PD-1/PDL-1 inhibitor-induced hypophysitis (2, 3). This review discusses recent findings on the underlying mechanism of autoimmune hypopituitarism.

Lymphocytic hypophysitis (autoimmune hypophysitis)

Lymphocytic hypophysitis is the most common form of hypophysitis and lymphocytic adenohypophysitis associated with pregnancy. Lymphocytic adenohypophysitis develops in 30–70% of patients during pregnancy or postpartum. (8). In contrast, lymphocytic infundibulo-neurohypophysitis and panhypophysitis do not show sex predominance (9). Lymphocytic hypophysitis is frequently associated with other autoimmune diseases, such as autoimmune thyroiditis, in up to 50% of the patients. The autoimmune etiology has been strongly suggested because of the presence of autoantibodies against α -enolase, GH, pituitary gland-specific factors 1a and 2 (PGSF1a and PGSF2), regulatory prohormone-processing enzymes commonly produced in the pituitary gland (PC1/3, PC2, CPE, and 7B2), secretogranin II, chromosome 14 open reading frame 166 (C14orf166), corticotroph-specific transcription factor Tpit, and human chorionic somatomammotrophin (HCS) (10). However, most of these antibodies are considered to be produced as a result of disruptions in the pituitary tissue.

Recently, anti-rabphilin antibodies have been found to be a biomarker for lymphocytic infundibulo-neurohypophysitis (11). Rabphilin-3A is expressed in the neurohypophysis and AVP neurons in the supraoptic nucleus in the hypothalamus. Immunization of mice with rabphilin-3A protein led to neurohypophysitis, and there was a linear association between the number of T cells that reacted with rabphilin-3A in peripheral blood mononuclear cells and that of CD3⁺ T cells infiltrating the neurohypophysis (12). These data suggest that the breakdown of immune tolerance to rabphilin-3A might cause infundibulo-neurohypophysitis.

Other animal models of autoimmune hypophysitis demonstrated continuous generation of autoreactive T and B cells within the pituitary gland (13). These infiltrating cells expressed IFN- γ and IL-17, both of which are involved in the pathogenesis of other autoimmune disease such as thyroiditis, multiple sclerosis, and type-1 diabetes. Proliferation of T cells in the pituitary was also reported in patients with autoimmune hypophysitis (13). It has also been reported that pregnant patients with hypophysitis showed abundant CD8⁺ T cells with activated phenotype (granzyme B⁺) in the pituitary (14).

In terms of genetic pathophysiology, it has been reported that the HLA markers, DQ8 and DR53, were strongly associated with autoimmune hypophysitis. The odds ratio of a patient with autoimmune hypophysitis expressing the HLA-DQ8 marker was 23-fold higher than that of a patient with another type of sellar mass (15). These associations suggest the importance of antigen presentation to T cells in the pathogenesis of autoimmune hypophysitis. Collectively, these data suggest that activated T cells play an important role in the development of lymphocytic hypophysitis.

IgG4-related hypophysitis

Patients with IgG4-RD, either synchronously or metachronously, show diffuse or focal organ enlargement and mass-forming or nodular/thickened lesions of various organs with abundant infiltration of IgG4-positive plasma cells with fibrosis (16). IgG4-RD plays a role in the disorders of a wide variety of organs, including Mikulicz's disease, autoimmune pancreatitis, hypophysitis, Riedel thyroiditis, interstitial pneumonitis, interstitial nephritis, prostatitis, lymphadenopathy, retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pseudotumors.

IgG4-related hypophysitis is a newly discovered subtype of hypophysitis that forms part of an emerging

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group of IgG4-RDs characterized by a combination of dense infiltration of IgG4-positive plasma cells into the pituitary gland, thickening of the pituitary stalk, diffuse infiltration of the pituitary with lymphocytes, fibrosis with a 'storiform' pattern, and increased serum IgG4 levels. It generally occurs in elderly men, involving either the anterior or posterior pituitary, and shows good response to steroid therapy (4, 17). Although considered a rare condition, it has been reported that the prevalence of IgG4-related hypophysitis in IgG4-RD (autoimmune pancreatitis) may be underestimated (18). The involvement of various organs was noted throughout the clinical course of IgG4-related hypophysitis, with retroperitoneal fibrosis being the most common form (38%), followed by interstitial pneumonia (28%), Mikulicz's disease and autoimmune pancreatitis (AIP; 24%), and lymph node swelling (18%). A small proportion of patients (14%) solely exhibited hypophysitis (18).

Regarding the pathogenesis, although data specific for IgG4-related hypophysitis have rarely been reported, accumulating evidence on IgG4-RD indicates autoimmune disease. For example, various autoantibodies have been detected in patients with IgG4-RD, including those against prohibitin, galectin-3, annexin A11, and laminin 511 E8; although some of these autoantibodies may play a pathogenic role, IgG4-type autoantibodies have not been detected in patients with IgG4-RD. Thus, the idea that autoantibodies play a major role in IgG4-RD has been questioned (19), but some of the autoantibodies may be involved in tissue-specific injury.

Several studies have suggested the involvement of genetic factors in IgG4-RD. A haplotype consisting of MHC class II alleles HLA-DRB1*04:05 and DQB1*04:01 has been reported to be associated with autoimmune pancreatitis. Involvement of *HLA*, Fc receptor-like 3 (*FCRL3*), cytotoxic T-lymphocyte-associated 4 (*CTLA4*), and potassium voltage-gated channel subfamily A member 3 (*KCNA3*) locus has also been suggested to play a role in IgG4-RD (20). Recently, a genome-wide association study involving Japanese individuals revealed *HLA-DRB1* and *FCGR2B* regions as the susceptibility loci for IgG4-RD (21). The genetic associations between *HLA-DRB1* and IgG4-RD have highlighted the fundamental role of the HLA locus in the onset like other autoimmune or allergic diseases, such as asthma. Indeed, one-third of IgG4-RD patients have a history of atopic disease including asthma, allergic rhinitis, and atopic dermatitis, and elevated levels of serum IgE levels are frequently observed (22). *FCγR2B* is the only *FCGR* family member expressed in B cells and is an inhibitory *FCγ* receptor. It plays an important role in the

elimination of autoreactive B cells. The SNP in the *FCGR2B* regions had an impact on *FCγR2B* expression, suggesting that the SNP is involved in the pathogenesis (21).

Various immunological abnormalities have been reported in patients with IgG4-RD. The increase in the number of T helper 2 (Th2) cells and regulatory T (Treg) cells plays an important role in the development of IgG4-related pancreatitis and cholangitis (23). Several reports demonstrated that Th2-dominant immune responses and the production of Th2-type cytokines (IL-4, IL-5, and IL-13), regulatory cytokine IL-10, and fibroblast-stimulating cytokine TGF- β are increased in IgG4-RD (24, 25). Functional abnormalities in CD4⁺ T cells, T follicular helper (Tfh) cells (26), and CD4⁺ cytotoxic T cells (27) have also been reported. Interestingly, patients with IgG4-RD often have phenotypes opposite to those observed in patients with other autoimmune diseases (e.g. increased number of Treg cells and augmentation of inhibitory cytokines such as IL-10 and TGF- β) (23), suggesting that the increase in serum IgG4 concentrations is a secondary response, since IgG4 is known to inhibit allergic phenotypes (28). Regarding inflammation and fibrosis, the involvement of elevated IFN-I-dependent IL-33 production has been suggested (29).

With respect to the increased serum concentration of IgG4 and tissue infiltration of IgG4-positive plasma cells, it has been reported that the expression of IL-10 and activation-induced cytidine deaminase (AID) was higher in patients with IgG4-RD than in patients with Sjogren's syndrome and in the controls (30). Since AID and IL-10 as well as Th2 cytokines can induce IgG4- and IgE-specific class-switch recombinations, overexpression of these factors may be involved in the pathogenesis of IgG4-RD through an IgG4-specific class-switch recombination (31). These observations suggest an important aspect of the pathogenesis of IgG4-RD, namely that the hyperproduction of IgG4 is frequently associated with allergy (32), suggesting a characteristic of allergic disease. Recently, both IgG4- and IgE-iso-type antibodies against galectin-3 produced by plasmablasts clones have been reported in patients with IgG4-RD (33). Although further investigation is required, the mechanism underlying isotype switching of immunoglobins to IgG4/IgE may be important in the pathogenesis of IgG4-RD (19).

ICI-induced hypophysitis

Immune checkpoint inhibitors (ICIs), such as anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4), anti-programmed cell

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death 1 (PD-1), and anti-programmed death 1 ligand 1 (PDL-1), have become the mainstay of treatment for various cancers (34). By increasing the activity of the immune system, treatment with ICIs is associated with a specific toxicity profile, often termed as an irAE (35). Although any organ system can be affected, irAE commonly involves the gastrointestinal tract, endocrine glands, skin, and liver (36). In terms of endocrinopathies, the involvement of various organs, including the thyroid, pituitary, adrenal, pancreas, parathyroid (37), and adipose tissue (38), has been reported (39). Importantly, the profile of endocrine irAE is different depending on each ICI that was used (as in isolation or with combination therapy). Because of the emerging topics, the underlying mechanisms and management for ICI-induced hypophysitis have recently been reviewed (2, 3, 40). With the use of CTLA-4 inhibitors, hypophysitis is predominantly observed in 8–13% of the patients (2, 39). In contrast, with PD-1/PDL-1 inhibitors, thyroiditis is predominant and hypophysitis is relatively rare (0.1–0.4%) (40). The incidence of hypophysitis was 8.5–9.0% when a combination of CTLA4 and PD1 inhibitors was used (41). Interestingly, a correlation seems to exist between overall patient survival and the incidence and severity of irAE. For example, these observations were noted in patients with hypophysitis treated with ipilimumab-induced hypophysitis (42) and in patients with thyroiditis (43).

The other important issue is the difference in the onset of hypophysitis and profile of the impaired hormone. The median time to occurrence is 2–4 months with CTLA-4 inhibitors, 3–6 months with PD-1 inhibitors, up to 1 year with PDL-1 inhibitors (44), and earlier for those on combination treatment (30 days on average) (40). ACTH and/or TSH deficiency are the most common pituitary hormone abnormalities followed by LH and FSH deficiency with the use of CTLA-4 inhibitors. Generally, ACTH deficiency is permanent, and the recovery of thyroid and gonadal axis has been reported. Mid-to-moderate diffuse enlargement of the pituitary gland, with either homogenous or heterogenous enhancement after contrast administration is typically observed in patients with CTLA-4 inhibitor-induced hypophysitis. In contrast, permanent and exclusive ACTH deficiency is observed and obvious enlargement of the pituitary is rare with the use of PD-1/PDL-1 inhibitors (40). These data strongly suggest the difference in the underlying mechanisms of CTLA-4 and PD-1/PDL-1 inhibitors.

The mechanisms that lead to irAE are still largely unclarified; however, several potential mechanisms such as T-cell activity against antigens present in tumors and

healthy tissue (molecular mimicry), increasing levels of preexisting autoantibodies (enhancement of preexisting autoimmunity), increasing levels of inflammatory cytokines (activation of immune response), and enhanced complement-mediated inflammation due to direct binding of the antibody with CTLA4 with CTLA4 expressed on normal tissue (direct action of the antibody) have been proposed (35).

Interestingly, CTLA4 is expressed in the anterior pituitary cells, and a similar feature of type II hypersensitivity in CTLA-4 inhibitor-induced hypophysitis was observed in an animal model, where complement-dependent cell injury occurred after the binding of anti-CTLA-4 antibodies to the cells (45). CTLA-4 is also expressed in normal human pituitary and pituitary adenomas, with different expression levels, which may explain the risk of hypophysitis (46). Importantly, with the use of CTLA-4 inhibitors, the subclass of ipilimumab is IgG1 and that of tremelimumab is IgG2, which can activate the classical complement pathway and lead to antibody-dependent cell-mediated cytotoxicity (40). An autopsy study of a patient with CTLA-4 inhibitor-induced hypophysitis revealed a strong expression of CTLA-4 in the anterior pituitary cells and similar features as type II hypersensitivity reactions (47). In contrast, PD-1 is not expressed in the pituitary, and PD-1 and PDL-1 inhibitors fall under the IgG4 subclass that cannot activate the classical complement pathway; therefore, different mechanisms have been suggested for PD-1/PDL-1 inhibitors. These different mechanisms may also explain the higher prevalence of hypophysitis with the use of CTLA4 inhibitors than with PD-1/PDL-1 inhibitors (39).

Several autoantibodies against anterior pituitary cells have been reported in patients with ICI-induced hypophysitis. Autoantibodies against TSH-, FSH-, or ACTH-producing cells have been detected in patients with ipilimumab-induced hypophysitis (45). A screening using cDNA expression libraries of the plasma samples identified anti-olfactory type G-protein alpha-activating polypeptide (GNAL) antibody and anti-integral membrane protein 2B (ITM2B) antibody in ICI-induced hypophysitis (48). Although the pathophysiological role of these antibodies is still unclarified, it has been suggested that the anti-GNAL autoantibody has the potential to act as both a predictive and an on-treatment biomarker for ICI-induced hypophysitis, whereas the anti-ITM2B autoantibody has the potential to act as an on-treatment biomarker for ICI-induced hypophysitis (48).

Specific hormone deficiencies associated with pituitary autoimmunity

Except for an isolated ACTH deficiency, isolated anterior pituitary hormone deficiencies without genetic defects are rare. In these conditions, the role of autoimmune mechanisms has strongly been suggested. For example, anti-pituitary antibodies against gonadotropin-secreting cells have been detected in patients with idiopathic hypogonadotropic hypogonadism (49). Anti-pituitary antibodies were present at high titers in 15%, 20%, and 21% of the patients with ACTH deficiency, GH deficiency, and hypogonadotropic hypogonadism, respectively, and these antibodies were targeted against corticotrophs, somatotrophs, and gonadotrophs, respectively (50). Furthermore, the presence of anti-somatotroph antibodies has been reported in some cases of idiopathic GH deficiency, both in adults and children (51, 52). However, the pathological significance and causal role of these antibodies have not been clarified.

Anti-PIT-1 hypophysitis (anti-PIT-1 antibody syndrome) is a newly described pituitary autoimmune disease characterized by acquired and specific GH, PRL, and TSH deficiencies (7, 53). This disorder is associated with a thymoma or neoplasm that ectopically expresses the PIT-1 protein (54). Circulating anti-PIT-1 antibody is a disease marker, and PIT-1-reactive cytotoxic T cells (CTLs) play a pivotal role in disease development (55). Because PIT-1 is an essential transcription factor in the differentiation and maintenance of GH-, PRL-, and TSH-producing cells, autoimmunity to PIT-1 is considered to play a causal role (54). Accumulating evidence has indicated that anti-PIT-1 hypophysitis is a thymoma-associated autoimmune disease like myasthenia gravis and is a form of paraneoplastic syndrome. Recently, the diagnostic criteria have been proposed (54).

In isolated ACTH deficiency, given that corticotrophs are often the first cell type to be affected in lymphocytic hypophysitis and that some cases of isolated ACTH deficiency are related to autoimmune diseases including autoimmune polyglandular syndrome, autoimmunity to corticotrophs has strongly been suggested as the pathogenesis (56). Indeed, anti-corticotroph antibodies have been detected in some patients. Among these autoantibodies, the causal involvement of anti-Tpit antibody in the development of lymphocytic hypophysitis has been speculated because Tpit is an essential transcription factor for the development of corticotrophs; however, this antibody is not specific to

lymphocytic hypophysitis, as it has also been detected in other autoimmune endocrine diseases (57). Further investigation is necessary to elucidate the significance of anti-Tpit antibody (6).

DAVID (deficient anterior pituitary with variable immune deficiency) syndrome is a rare disorder first described in 2012 (58). The patients from three distinct kindreds presenting with symptomatic ACTH deficiency preceded by hypogammaglobulinemia and recurrent infections. In this syndrome, patients manifest isolated early-onset ACTH deficiency, which is a rare condition. Whole exome analysis revealed germline heterozygous mutations affecting the C-terminal part of *NFKB2* in several unrelated patients (59). As the underlying mechanism, the mutation in *NFKB2* resulted in an impaired B cell function leading to common variable immunodeficiency (CVID); although autoimmunity may be related, the underlying mechanisms in ACTH deficiency remain unknown.

Recently, a case of isolated ACTH deficiency as a form of paraneoplastic syndrome was reported (60). Interestingly, the patients had large-cell neuroendocrine carcinoma with ectopically expressed proopiomelanocortin (POMC) in the lung and circulating anti-POMC antibodies; POMC-reactive CTLs were also detected. Given that CTL infiltration around corticotrophs was also observed in another case of ectopic ACTH syndrome, it has been suggested that isolated ACTH deficiency is associated at least in part with paraneoplastic syndrome (54). Generally, ectopic ACTH expression in a tumor is associated with ectopic ACTH syndrome with excessive ACTH that manifests as Cushing's syndrome. Interestingly, silent POMC expression was observed in 48% of the patients with non-small-cell lung cancer (61) and with carcinoid tumors without ectopic ACTH syndrome (62), suggesting that silent ectopic ACTH expression is not rare. Limited or bioinactive ectopic expression of POMC may cause an immune reaction to POMC-expressing cells including corticotrophs, but not hormone excess. Furthermore, these observations that especially silent ectopic POMC expression is not rare in tumors may explain the reason behind the relatively high prevalence of isolated ACTH deficiency as compared to conditions with other isolated anterior pituitary hormone deficiencies. Although various underlying mechanisms of pituitary autoimmunity have been proposed, these results suggest the importance of paraneoplastic syndrome as the cause of pituitary autoimmune diseases (54).

Conclusion

New clinical entities in autoimmune pituitary disease have recently emerged. In particular, studies on ICI-induced hypophysitis certainly give an important clue to the underlying mechanisms that evoke autoimmunity to the pituitary gland. In addition, the concept of paraneoplastic syndrome also highlights a new aspect. Diverse approaches are necessary for clarifying the pathophysiology.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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