A Case of IgG4-Related Hypophysitis Without Pituitary Insufficiency

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Context: IgG4-related hypophysitis is a novel clinical disease entity, which is typically complicated by hypopituitarism.

Objective: The objective of the study was to describe a novel case of IgG4-related hypophysitis without pituitary insufficiency and summarize the current relevant literature.

Patient and Methods: A 55-year-old Japanese man presented with an enlarged pituitary gland and bitemporal hemianopsia. Endocrine studies revealed normal pituitary function, although his serum IgG4 level was high. The patient underwent a transsphenoidal biopsy of the pituitary gland, and the pathological tissues were consistent with IgG4-related hypophysitis. Oral prednisolone therapy was started, and after 6 months, his serum IgG4 level decreased and visual field improved.

Conclusion: We described the first case of IgG4-related hypophysitis without pituitary insufficiency. However, further case collection is needed to characterize the pathophysiology of IgG4-related hypophysitis. (J Clin Endocrinol Metab 98: 1808–1811, 2013)

IgG4-related diseases, including IgG4-related hypophysitis, are a recently characterized entity marked by elevated serum IgG4 levels and tissue infiltration by IgG4-positive plasma cells, according to several review articles published in 2012 (1–3). Ever since autoimmune sclerosing pancreatitis was described in 2001 (4) as the first high-serum IgG4 case, several other cases with high serum IgG4 levels have been reported, mostly from Japan (5–10). During a Japanese consensus meeting in 2010, the term, IgG4-related disease, was selected from many suggestions to describe this disorder (2).

Since the first IgG4-related hypophysitis case was described in 2004 (11), more than 20 histogenetically proven cases have been reported, mostly from Japan (7–9, 12–25); however, all were accompanied by complications of pituitary insufficiency. Here, we describe a novel case of biopsy-proven IgG4-related hypophysitis without hypopituitarism.

Case reports

In February 2012, a 55-year-old Japanese man was referred to our department with an enlarged pituitary gland. His medical history included treatment at the department of internal medicine in 2005 for numbness in his feet, for which he underwent a magnetic resonance imaging (MRI) brain scan because microvascular infarction was suspected. Since then, he had been followed up with annual MRI brain scans but was not prescribed medication. In 2012 he began showing mild bitemporal hemianopsia, and an MRI revealed a mass-like en-
largetment of the pituitary gland, although no abnormality had been detected in his sella turcica prior to 2011. The patient also had a history of diffuse large B cell lymphoma in 2001, which was in chemotherapy-induced remission.

At the time of his hospital presentation, the patient was awake, alert, and oriented, and headache, fatigue, or polyuria was absent. His vital signs were as follows: temperature, 36.1°C; heart rate, 68 beats/min; and blood pressure, 104/60 mm Hg. His height was 178.5 cm and his weight was 81 kg. There were no characteristic physical findings and no signs of hyperpituitarism or hypopituitarism. In addition, no goiter or enlargement of the lymph nodes was noted. He did not have trouble with his eyesight and his spectacle-corrected visual acuity was 20/16 in both eyes, but a visual field test showed inferior and bitemporal visual field defects.

A 3-T MRI of the pituitary gland revealed enlargement of the posterior lobe and stalk (Figure 1A). In a T1-weighted image, a physiological posterior pituitary hyperintense spot was not clearly visualized, whereas the thickened pituitary stalk was uniformly enhanced after gadolinium administration and positioned adjacent to the optic chiasm.

On the basis of the clinical course and MRI imaging, we suspected infundibulohypophysitis. However, because germinoma, malignant lymphoma, granulomatous diseases such as sarcoidosis and tuberculosis (TB), autoinflammatory disease, and rheumatoid disease needed to be ruled out in cases of mass-like enlargement of the pituitary gland, we performed a blood analysis and used other imaging tests to clarify the diagnosis.

Laboratory results revealed the following: serum sodium, 139 mEq/L; potassium, 4.1 mEq/L; chloride, 107 mEq/L; C-reactive protein, 0.07 mg/dL; IgG, 2388 mg/dL (reference range 880-1800 mg/dL); and IgG4, 1010 mg/dL (reference range 4–108 mg/dL). We observed normal levels of autoimmune antibodies, including anti-Sjögren’s syndrome (SS)-A/Ro and anti-ss-B/La antibodies, and those for human chorionic gonadotropin-β, soluble IL-2 receptor, IL-6, adenosine deaminase, angiotensin I-converting enzyme, and tumor markers such as α-fetoprotein. In addition, a QuantiFERON TB-2G test (Cellestis Ltd, Carnegie, Australia) was negative for active TB.

On his initial visit, an endocrine assessment revealed normal pituitary function: ACTH, 52.5 pg/mL; cortisol, 13.1 µg/dL; TSH, 3.91 mIU/L; GH, 0.07 ng/mL; IGF, 122 ng/mL, LH, 10.4 mIU/mL; FSH, 51.4 mIU/mL; prolactin (PRL), 13.8 ng/mL; and T, 273 ng/dL (reference range 250-1100 ng/dL). Subsequent hormonal provocative tests revealed that the cortisol response to CRH, GH response to GH-releasing hormone (GRH), TSH, and PRL response to TRH, and LH and FSH response to LHRH were all normal (Table 1). An insulin tolerance test and a GH-releasing peptide-2 infusion test were also performed and both showed normal responses of the pituitary gland (data not shown).

Computed tomography results of the patient’s chest and abdomen were normal. Whole-body fluorodeoxyglucose positron emission tomography showed increased fluorodeoxyglucose uptake in the lymph nodes of the neck, mediastinum, and inguinal area; however, no significant findings were detected in the brain and retroperitoneal area.

The patient’s test results strongly favored a diagnosis of IgG4-related hypophysitis, although pituitary insufficiency was not observed. Hence, we scheduled a pituitary biopsy for diagnostic purposes, and in April 2012, a transsphenoidal sampling of the pituitary was performed, with-

![Figure 1.](https://example.com/figure1.png)
out administering any steroids before biopsy. Upon entering the sella turcica, normal dura mater and the anterior lobe of the pituitary were noted, but the posterior lobe was relatively whitish in color and harder than the normal pituitary tissue. Immediately after the biopsy, a physiological dose of hydrocortisone was administered. The patient experienced no postoperative complications, including diabetes insipidus, during the perioperative period. One month after the biopsy, hormonal stimulating tests were performed and all showed normal responses of the pituitary, similar to the preoperative period (data not shown).

The pathological findings of the pituitary revealed that the anterior lobe tissue was normal; however, the posterior lobe specimen revealed inflammatory cell infiltration (Figure 2A) of mostly CD3-positive T lymphocytes, although CD20-positive B lymphocytes were also observed to a lesser extent (T lymphocyte to B lymphocyte ratio was 3:1). Many plasma cells and Russell bodies were distinct and the number of κ- and λ-light chains was the same (data not shown). There were more than 10 IgG4-positive plasma cells per high-power field (HPF), which accounted for greater than 50% of the IgG-positive plasma cells (Figure 2B).

The high-serum IgG4 level and enlargement of the pituitary supported a diagnosis of IgG4-related hypophysitis, which was confirmed by pathological findings. After postoperative hormonal stimulation assessment, the patient was started on oral prednisolone (PSL) at 50 mg/d, which was tapered to 10 mg/d over a 5-week period. Subsequently the patient was prescribed PSL at 10 mg/d, and his hemianopsia improved. The size of the posterior lobe and stalk of the pituitary were significantly decreased (Figure 1B), which was accompanied by a decrease in serum IgG4 level. After 6 months of PSL administration, laboratory results revealed an IgG level of 1430 mg/dL and IgG4 of 457 mg/dL, although the levels of other immunoglobulin subclasses remained unchanged.

Discussion

Herein we report a case of biopsy-proven IgG4-related hypophysitis with normal pituitary function. Because of the novel concept of IgG4-related hypophysitis, there are no established diagnostic criteria. In 2011 Leporati et al (22) suggested 5 criteria to diagnose IgG4-related hypophysitis: criterion 1, mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with more than 10 IgG4-positive cells per HPF; criterion 2, a sellar mass and/or thickened pituitary stalk on pituitary MRI when pituitary histopathology is unavailable; criterion 3, biopsy-proven IgG4-positive lesions in other organs; criterion 4, increased serum IgG4 level (>140 mg/dL); and criterion 5, shrinkage of the pituitary mass and symptom improvement with steroids. Leporati et al (22) also proposed that the diagnosis of IgG4-related hypophysitis is established when any of the following is fulfilled: criterion 1 alone or criterion 2 + 3 or criterion 2 + 4 + 5. According to the criteria, a pituitary biopsy is not essential; however, there have been 8 case reports diagnosed by pituitary biopsy (12, 13, 16–19, 22).

Our patient fulfilled the suggested diagnostic criteria and, interestingly, did not show hypopituitarism, although all previously reported cases of hypophysitis were associated with the complication of pituitary insufficiency. Although it is uncertain why we observed normal pituitary functions in our patient, a likely explanation is that our patient underwent an annual brain scan and the pituitary lesion was detected before the onset of hypopituitarism. At the present time, the pathogenetic mechanism and underlying immunological abnormalities remain unclear (2). A recent report identified autoimmune antibodies against GH and ACTH in a patient with IgG4-related hypophysitis (26). Nonetheless, collecting further evident cases and analysis is required to characterize the pathophysiology of IgG4-related hypophysitis.

The typical therapy for IgG4-related hypophysitis is undefined; however, glucocorticoids are recommended as a first-line therapy against IgG4-related disease (12). On the basis of treatment of autoimmune pancreatitis, an initial oral PSL dose of 0.6 mg/kg for 2–4 weeks is suggested, which is then tapered by 5 mg every 1–2 weeks for 2–3 months to determine a maintenance dose (2.5–5 mg/d).
which should be discontinued within 3 years (12, 27). Our patient received the recommended initial PSL dose, which was tapered on the basis of changes in clinical manifestations, biochemical blood tests (including IgG4 level), and repeated imaging findings. At present, we have followed up our patient for 6 months and report no signs of recurrence.

In conclusion, we reported the first known patient with IgG4-related hypophysitis without pituitary insufficiency. After the initiation of PSL administration, the patient’s pituitary gland enlargement was significantly ameliorated and his serum IgG4 level decreased. We intend to continue following up this patient. This case suggests that when clinicians detect an enlarged pituitary, even if the patient has normal pituitary function, serum IgG4 measurement for early diagnosis of IgG4-related hypophysitis should be performed.

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References