Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9365-22
Intern Med 61: 3541-3545, 2022
http://internmed.jp

【 CASE REPORT 】

Central Diabetes Insipidus Due to IgG4-related Hypophysitis That Required over One Year to Reach the Final Diagnosis Due to Symptoms Being Masked by Sialadenitis

Yuichiro Iwamoto, Shigehito Mori, Fuminori Tatsumi, Toshitomo Sugisaki, Kazunori Dan, Yukino Katakura, Tomohiko Kimura, Masashi Shimoda, Shuhei Nakanishi, Tomoatsu Mune and Hideaki Kaneto

Abstract:

Pituitary inflammation due to IgG4-related disease is a rare condition and is sometimes accompanied by central diabetes insipidus. Central diabetes insipidus produces a strong thirst sensation, which may be difficult to distinguish when complicated by salivary insufficiency. A 45-year-old man was admitted to our department for a thorough examination of his thirst and polyuria. He had suddenly developed these symptoms more than one year earlier and visited an oral surgeon. Swelling of the left submandibular gland, right parotid gland, and cervical lymph nodes had been observed. Since his IgG4 level was relatively high at 792 mg/dL and a lip biopsy showed high plasmacytoid infiltration around the gland ducts, he had been diagnosed with IgG4-related disease. He had started taking 0.4 mg/kg/day of prednisolone, and his chief complaint temporarily improved. However, since the symptom recurred, he was referred to our institution. After admission, to examine the cause of his thirst and polyuria, we performed a water restriction test, vasopressin loading test, hypertonic saline loading test and pituitary magnetic resonance imaging. Based on the findings, we diagnosed him with central diabetes insipidus due to IgG4-related hypophysitis. We increased the dose of prednisolone to 0.6 mg/kg/day and started 10 μg/day of intranasal desmopressin. His symptoms were subsequently alleviated, and his serum IgG4 level finally normalized. We should remember that IgG4-related disease can be accompanied by hypophysitis and that central diabetes insipidus is brought about by IgG4-related hypophysitis. This case report should remind physicians of the fact that pituitary inflammation due to IgG4-related disease is very rare and can be masked by symptoms due to salivary gland inflammation, which can lead to pitfalls in the diagnosis in clinical practice.

Key words: IgG-related disease, hypophysitis, central diabetes insipidus, steroid therapy, vasopressin

(Intern Med 61: 3541-3545, 2022)
(DOI: 10.2169/internalmedicine.9365-22)

Introduction

Pituitary inflammation due to IgG4-related disease is a rare condition and is associated with central diabetes insipidus in 17.9% of patients (1). IgG4-related hypophysitis usually shows a good response to steroid therapy, but in some cases, recurrence is observed, leading to an irreversible phase, or else long-term hormone replacement therapy is necessary (2).

Central diabetes insipidus is typically characterized by sudden onset of polyuria and intolerable thirst (3). In central diabetes insipidus patients, biosynthesis and/or secretion of vasopressin is reduced, leading to a decrease in urine osmolality. Desmopressin acetate is often used to treat the disease.

Division of Diabetes, Endocrinology and Metabolism, Kawasaki Medical School, Japan
Received: January 10, 2022; Accepted: April 5, 2022; Advance Publication by J-STAGE: May 14, 2022
Correspondence to Dr. Yuichiro Iwamoto, iwamoto.g@med.kawasaki-m.ac.jp

IgG4-related diseases are frequently associated with bilateral submandibular adenitis, and thirst occurs in 30% of cases (4). Similar symptoms are observed in subjects with central diabetes insipidus. Abnormal findings in the pituitary area were reportedly found along with abnormalities in other organs, such as the pancreas and submandibular gland, in some subjects with IgG4-related hypophysitis (5-7); however, in other subjects with IgG4-related hypophysitis, the abnormal findings in the pituitary area were only noted several years after the diagnosis of abnormalities in other organs (9-11).

We experienced a case of central diabetes insipidus in which it took more than one year to reach final diagnosis because the symptoms were masked by IgG4-related sialadenitis.

Case Report

A 45-year-old man was admitted to our department for a thorough examination of an increase in urine volume. He had suddenly developed thirst and polyuria 440 days ago and begun to drink about 8 L of water per day. When the thirst did not subside and he visited an oral surgeon 338 days ago, swelling of the left submandibular gland, right parotid gland, and cervical lymph nodes were observed. Computed tomography (CT) showed diffuse enlargement of the pancreas, and blood tests showed high levels of IgG4 (IgG4, 792 mg/dL). A biopsy of the lip was performed, which revealed high plasmacytoid infiltration around the gland ducts and more than 200 IgG4-positive plasmacytoid cells/high-power field (HPF), leading to a diagnosis of IgG4-related disease.

The patient started taking 30 mg/day of prednisolone (0.4 mg/kg/day) at the Department of Collagen Disease. He mentioned that his chief complaint was temporarily improved, but we did not necessarily believe that the disease had actually resolved. Indeed, his symptoms recurred after about one month, and he was referred to our institution for a thorough examination. At the time of admission, he was being treated with prednisolone 5 mg/day.

On admission, a physical examination revealed a blood pressure of 148/97 mmHg, a pulse rate of 72 beats/min, and a body temperature of 36.9°C. His height and body weight were 175.5 cm and 75.7 kg. On an examination of the neck, enlarged parotid and submandibular glands and cervical lymph nodes were palpated. There were no abnormal findings in the hemogram and electrocytes. Liver dysfunction was observed (γ-GTP, 194 U/L; AST, 22 U/L; ALT, 33 U/L), and the renal function was within normal range. Serum sodium, plasma osmolality, and serum arginine vasopressin (AVP) were 140 mmol/L, 287 mOsm/kg, and 0.5 pg/mL, respectively. Anterior pituitary hormones were normal as follows: adrenocorticotropic hormone (ACTH) 19.1 pg/mL, cortisol 16.6 μg/dL, growth hormone 0.30 ng/mL, insulin-like growth factor 1 124 ng/mL, prolactin 13.9 ng/mL, thyroid-stimulating hormone 0.93 μIU/mL, free T3 3.73 pg/mL, free T4 1.01 ng/dL, follicle-stimulating hormone 7.08 mIU/mL, luteinizing hormone 3.64 mIU/mL, and free testosterone 9.5 pg/mL. There were no abnormalities in diabetes or lipid markers. Immunological tests showed high levels of IgG4 (IgG4, 241 mg/dL). On a urinalysis, the urine specific gravity was 1.003, and the urine osmolality was 115 mOsm/kg. The urine volume for the first 24 h after admission was 7,900 mL.

There were findings of hypotonic polyuria. Since central diabetes insipidus was suspected, additional tests were performed. In the water restriction test, the urine osmolality was 90 mOsm/kg at the start and still less than 300 mOsm/kg after 360 minutes (Fig. 1A). The water restriction test showed a weight loss of 2.18%. In the desmopressin loading test, the urine osmolality was more than 300 mOsm/kg at 30 minutes after subcutaneous injection of 5 units of desmopressin (Fig. 1B). Hypertonic saline infusion test showed no reactive secretion of vasopressin in response to an increased serum sodium concentration (Fig. 1C). Based on these findings, we diagnosed him with central diabetes insipidus.

Pituitary magnetic resonance imaging (MRI) showed a decreased intensity of the posterior lobe of the pituitary gland (Fig. 2A) and thickening of the pituitary stalk on T1-weighted imaging (Fig. 2B), leading to the diagnosis of central diabetes insipidus due to IgG4-related hypophysitis. The dose of prednisolone was increased to 0.6 mg/kg/day, and 10 μg/day of intranasal desmopressin was started; consequently, the urine output decreased rapidly. Two months after being discharged from the hospital, the patient's serum IgG4 was <100 mg/dL in the outpatient clinic.

Discussion

IgG4-related hypophysitis is a rare disease, with only 84 cases reported thus far, and 70.2% of cases of IgG4-related pituitary inflammation induce ADH deficiency symptoms. Most instances of IgG4-related pituitary inflammation induce panhypopituitarism, while 17.9% of cases are associated with central enuresis (1). Leporati et al. proposed diagnostic criteria for IgG4-related hypophysitis (5). In the present case, multiple organ enlargements, including that of the submandibular gland, parotid gland, cervical lymph nodes, and pancreas, were observed, and an elevated serum IgG4 level, high plasma cell infiltration around the gland ducts, and many IgG4-positive plasma cells were found on a lip biopsy. We therefore diagnosed this patient with IgG4-related disease (6). Furthermore, pituitary MRI showed a mass shadow in the sella turcica, and enlargement of the pituitary stalk was also confirmed. Based on these findings, we diagnosed this patient with IgG4-related pituitary inflammation.

In the present case, it took over one year to reach the final diagnosis of central diabetes insipidus due to IgG4-related hypophysitis. Abnormal findings in the pituitary area were reportedly found together with abnormalities in other organs, such as the pancreas and submandibular gland, in

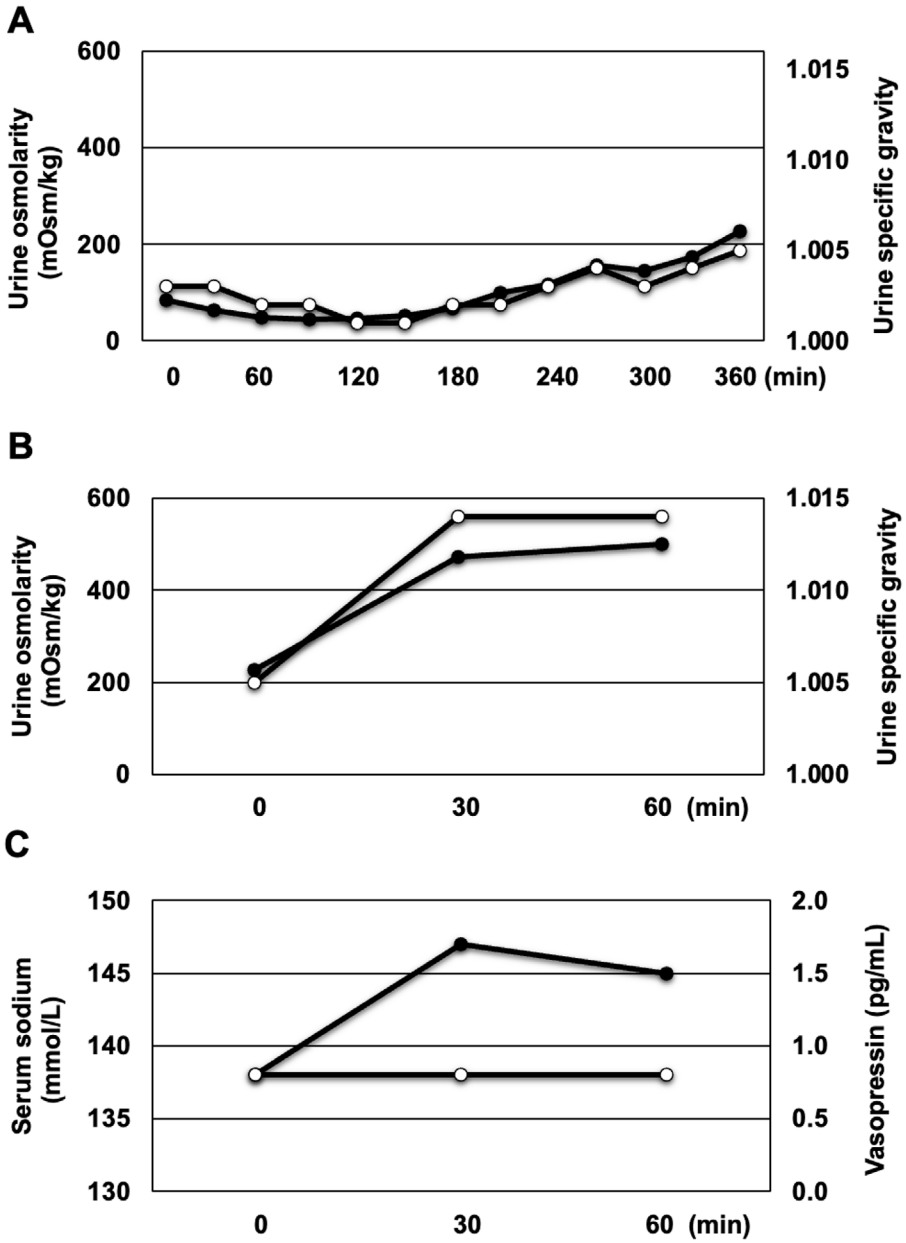

Figure 1. **(A) On a water restriction test, the urine osmolality was 90 mOsm/kg at the start and still <300 mOsm/kg after 360 minutes. The water restriction test showed a weight loss of 2.18%. Closed circle, urine osmolarity; open circle, urine specific gravity. (B) In the vasopressin loading test, the urine osmolality was >300 mOsm/kg at 30 minutes after subcutaneous injection of 5 units of desmopressin. Closed circle, urine osmolarity; open circle, urine specific gravity. (C) The hypertonic saline loading test showed no reactive secretion of vasopressin in response to an increased serum sodium concentration. Closed circle serum sodium; open circle, vasopressin.**

some subjects with IgG4-related hypophysitis (9-12). However, in other cases, abnormal findings in the pituitary area were found several years after the diagnosis of abnormalities in other organs (5, 6, 13). Regarding central diabetes insipidus due to IgG4-related hypophysitis, there is substantial variation in the period between the diagnosis of central diabetes insipidus and the diagnosis of abnormality in other organs (6, 12).

IgG4-related hypophysitis recurs during the tapering phase and has an irreversible course, in some cases requiring long-term hormone replacement therapy. In the present case, the patient himself clearly remembered the timing of the onset of the disease, and it took more than one year for a diagnosis to be reached even though he had typical symptoms of central diabetes insipidus. The first factor was that the patient had submandibular gland enlargement and parotid gland enlargement due to IgG4-related disease. The frequency of IgG4-related pituitary inflammation associated with systemic IgG4-related disease is 75%, and in this case, multiple organ enlargements of salivary glands, cervical

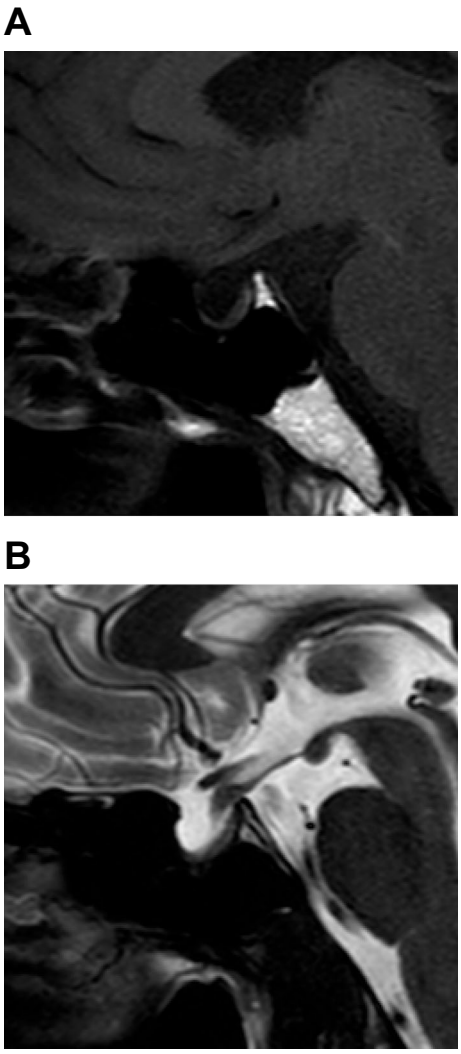

Figure 2. Pituitary MRI showed a decreased intensity of the posterior lobe of the pituitary gland (A) and thickening of the pituitary stalk on T1-weighted imaging (B).

lymph nodes, and the pancreas were observed. IgG4-related sialadenitis is a common complication of IgG4-related disease, and in 30% of cases, it is associated with thirst and decreased salivary flow (4). In patients with IgG4-related sialadenitis and central enuresis, it is difficult to determine the primary locus of the thirst sensation unless central enuresis caused by IgG4-related pituitary inflammation is included in the differential diagnosis. The second reason was that since this patient was quite optimistic, he did not feel that his thirst and polyuria were pathological. Central diabetes insipidus is usually caused by hypertonic dehydration due to polyuria, which stimulates the thirst center and induces drinking behavior due to unbearable thirst. In the present case, the patient was not aware of polyuria compared to his complaints of thirst, and one reason for the delay was that the patient's symptoms had temporarily improved with steroid treatment for IgG4-related disease.

It is recommended that the initial dose of treatment for IgG4-related hypopituitaritis be set at 0.6 mg/kg/day of prednisolone (2). Even if symptoms temporarily improve, there is a high probability that they will flare up with tapering. Therefore, a maintenance dose of prednisolone of ≥2.5 mg/day is recommended. However, the patient in this report relapsed after 1 month under treatment with prednisolone 5 mg/day. These findings indicate that the required maintenance dose of prednisolone varies depending on the pathogenesis of each patient, and steroid therapy with an insufficient dose does not lead to remission of symptoms in some cases. Indeed, it has been reported that glucocorticoid therapy to reduce inflammation is associated with a recovery of the pituitary function in some subjects (14-16). It has been also reported, however, that glucocorticoid therapy fails to perform well in other subjects (17-19). Furthermore, there have been several reports showing that lymphocytic hypophysitis remits spontaneously (20, 21), whereas for autoimmune pancreatitis caused by IgG4-related diseases, the recommended dose of prednisolone is 0.6 mg/kg/day or 30-40 mg/day (22). In the present case, the initial dose of prednisolone was set at 30 mg, according to the recommended dose for IgG4-related disease, but this equated to 0.4 mg/kg/day, which may have been an insufficient initial dose. After the diagnosis of central diabetes insipidus, the dose of prednisolone was increased to 0.6 mg/kg/day, and the serum IgG4 level improved to <100 mg/dL in 2 months. A dose of 0.6 mg/kg of body weight may be the ideal starting dose when IgG4-related hypophysitis is suspected.

Based on these findings, we should bear in mind the possibility that IgG4-related disease may be accompanied by hypophysitis and that central diabetes insipidus can be induced by IgG4-related hypophysitis. The rarity of such pituitary inflammation due to IgG4-related disease may represent a pitfall in the diagnosis of such conditions in clinical practice, and this case report will hopefully serve as a timely reminder for clinicians.

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

The authors state that they have no Conflict of Interest (COI).

References

1. Shikuma J, Kan K, Ito R, et al. Critical review of IgG4-related hypophysitis. Pituitary **20**: 282-291, 2017.
2. Takagi H, Iwama S, Sugimura Y, et al. Diagnosis and treatment of autoimmune and IgG4-related hypophysitis: clinical guidelines of the Japan Endocrine Society. Endocr J **67**: 373-378, 2020.
3. Garrahy A, Moran C, Thompson CL. Diagnosis and management of central diabetes insipidus in adults. Clin Endocrinol (Oxf) **90**: 23-30, 2019.
4. Fragoulis GE, Zampeli E, Moutsopoulos HM. IgG4-related sialadenitis and Sjögren's syndrome. Oral Dis **23**: 152-156, 2017.
5. Leporati P, Landek-Salgado MA, Lupi I, Chiovato L, Caturegli P. IgG4-related hypophysitis: a new addition to the hypophysitis spectrum. J Clin Endocrinol Metab **96**: 1971-1980, 2011.
6. Umehara H, Okazaki K, Kawa S, et al.; Research Program for Intractable Disease by the Ministry of Health, Labor and Welfare (MHLW) Japan. The 2020 revised comprehensive diagnostic

(RCD) criteria for IgG4-RD. Mod Rheumatol **31**: 529-533, 2021.
7. van der Vliet HJ, Perenboom RM. Multiple pseudotumors in IgG4-associated multifocal systemic fibrosis. Ann Intern Med **141**: 896-897, 2004.
8. Yamamoto M, Takahashi H, Ohara M, et al. A case of Mikulicz's disease (IgG4-related plasmacytic disease) complicated by autoimmune hypophysitis. Scand J Rheumatol **35**: 410-411, 2006.
9. Wong S, Lam WY, Wong WK, Lee KC. Hypophysitis presented as inflammatory pseudotumor in immunoglobulin G4-related systemic disease. Hum Pathol **38**: 1720-1723, 2007.
10. Isaka Y, Yoshioka K, Nishio M, et al. A case of IgG4-related multifocal fibrosclerosis complicated by central diabetes insipidus. Endocr J **55**: 723-728, 2008.
11. Tanabe T, Tsushima K, Yasuo M, et al. IgG4-associated multifocal systemic fibrosis complicating sclerosing sialadenitis, hypophysitis, and retroperitoneal fibrosis, but lacking pancreatic involvement. Intern Med **45**: 1243-1247, 2006.
12. Tsuboi H, Inokuma S, Setoguchi K, et al. Inflammatory pseudotumors in multiple organs associated with elevated serum IgG4 level: recovery by only a small replacement dose of steroid. Intern Med **47**: 1139-1142, 2008.
13. Hori M, Makita N, Andoh T, et al. Long-term clinical course of IgG4-related systemic disease accompanied by hypophysitis. Endocr J **57**: 485-492, 2010.
14. Nussbaum CE, Okawara SH, Jacobs LS. Lymphocytic hypophysitis with involvement of the cavernous sinus and hypothalamus. Neurosurgery **28**: 440-444, 1991.
15. Hashimoto K, Takao T, Makino S. Lymphocytic adenohypophysitis and lymphocytic infundibuloneurohypophysitis. Endocr J **44**: 1-10, 1997.
16. Kristof RA, Van Roost D, Klingmuller D, Springer W, Schramm J. Lymphocytic hypophysitis: noninvasive diagnosis and treatment by high dose methylprednisolone pulse therapy? J Neurol Neurosurg Psychiatry **67**: 398-402, 1999.
17. Reusch JE, Kleinschmidt-DeMasters BK, Lillehei KO, Rappe D, Gutierrez-Hartmann A. Preoperative diagnosis of lymphocytic hypophysitis (adenohypophysitis) unresponsive to short course dexamethasone: case report. Neurosurgery **30**: 268-272, 1992.
18. Nishioka H, Ito H, Miki T, Akada K. A case of lymphocytic hypophysitis with massive fibrosis and the role of surgical intervention. Surg Neurol **42**: 74-78, 1994.
19. Thodou E, Asa SL, Kontogeorgos G, Kovacs K, Horvath E, Ezzat S. Clinical case seminar: lymphocytic hypophysitis: clinicopathological findings. J Clin Endocrinol Metab **80**: 2302-2311, 1995.
20. Gagneja H, Arafah B, Taylor HC. Histologically proven lymphocytic hypophysitis: spontaneous resolution and subsequent pregnancy. Mayo Clin Proc **74**: 150-154, 1999.
21. Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune hypophysitis. Endocr Rev **26**: 599-614, 2005.
22. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. Gut **58**: 1504-1507, 2009.